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HEALTH-RELATED QUALITY OF LIFE AND PSYCHOLOGICAL DISTRESS IN PATIENTS WITH CORONARY HEART DISEASE

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“Everything will be okay in the end. If it's not okay, it's not the end.”

J. Lennon

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Abbreviations

A	
ACS	Acute Coronary Syndrome
AMI	Acute Myocardial Infarction
AQol	Assessment of Quality of Life
ASPIRE	Action on Secondary Prevention through Intervention to Reduce Events
B	
BDI	Beck Depression Inventory
BMI	Body Mass Index
BP	Blood Pressure
C	
CABG	Coronary Artery Bypass Graft Surgery
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CHD	Coronary Heart Disease
CI	Confidence Interval
CVD	CardioVascular Disease
D	
15D	15 Dimensional instrument
DALY	Disability Adjusted Life Year
DBP	Diastolic Blood Pressure
DSM	Diagnostic and Statistical manual of Mental disorders
E	
EQ-5D(-3L)	EuroQol 5 Dimensions (3 level)
EQ-5D$_{index}$	EuroQol utility value
EQ-VAS	EuroQol Visual Analogue Scale
ESC	European Society of Cardiology
EU	European Union
EUROASPIRE	EUROpean Action on Secondary and Primary prevention through Intervention to Reduce Events
G	
GDP	Gross Domestic Product
H	
HADS	Hospital Anxiety and Depression Scale
HADS-A	Anxiety dimension of the Hospital Anxiety and Depression Scale
HADS-D	Depression dimension of the Hospital Anxiety and Depression Scale

HbA1c	Glycated Haemoglobin
HDL-C	High-Density Lipoprotein Cholesterol
HRQoL	Health-Related Quality of Life
HUI	Health Utility Index

I

ICER	Incremental Cost-Effectiveness Ratio
IPAQ	International Physical Activity Questionnaire
IQOLA	International Quality Of Life Assessment

L

LDL-C	Low-Density Lipoprotein Cholesterol

M

MacNew	MacNew heart disease health-related quality of life questionnaire
MCS-12	SF-12 Mental Component Summary scale
MET	METabolic equivalent
MI	Myocardial Infarction
MID	Minimal Important Difference
MIDAS	Myocardial Infarction Dimensional Assessment Scale
MLHF	Minnesota Living with Heart Failure questionnaire

O

OR	Odds Ratio

P

PCI	Percutaneous Coronary Intervention
PCS-12	SF-12 Physical Component Summary scale
PHQ	Patient Health Questionnaire
PTCA	Percutaneous Transluminal Coronary Angioplasty

Q

QALY	Quality Adjusted Life Year
QWB-SA	Quality of Well-Being Scale

R

RMSEA	Root Mean Square Error of Approximation

S

SAQ	Seattle Angina Questionnaire
SD	Standard Deviation
SF-12(v2)	12-item Short Form Health Survey (second version)
SF-12/1	First question of SF-12 tool, asking about a patient's general health
SF-12/BP	SF-12 Bodily Pain dimension

SF-12/GH	SF-12 General Health dimension
SF-12/MH	SF-12 Mental Health dimension
SF-12/PF	SF-12 Physical Functioning dimension
SF-12/RE	SF-12 Role Emotional dimension
SF-12/RP	SF-12 Role Physical dimension
SF-12/SF	SF-12 Social Functioning dimension
SF-12/VT	SF-12 Vitality dimension
SF-36	36-item Short Form health survey
SF-6D	6-Dimensional health state classification

T

TC	Total Cholesterol
TLI	Tucker–Lewis Index

W

WHO	World Health Organisation

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Chapter 1. Introduction

During the last century, life expectancy has increased substantially worldwide. In Europe, the mean life duration has evolved from 65.6 years in the late 1950's to 76.5 years currently. At this rate, by 2095-2100, life expectancy across Europe will rise to 87.4 years (United Nations, 2013). This evolution can be partly explained by the drop in coronary heart disease (CHD) mortality rates during the latest decades. Nevertheless, CHD remains the most common cause of death in Europe, responsible for one out of every five lives lost (Nichols et al, 2012). A great variation in death rates exists across different geographical areas, with the highest rates observed in central and eastern European countries, and the lowest mortality rates seen in southern European countries (Nichols et al, 2012).

Likewise, CHD is also a major cause of morbidity. Population ageing is associated with an increase in number of patients suffering from coronary disease (Nichols et al, 2012). According to the WHO, 10% of all disability adjusted life years in Europe can be attributed to CHD (Nichols et al, 2012; World Health Organisation, 2013a).

Indeed, CHD remains a ubiquitous illness requiring expensive treatment. The economic burden associated with the disease rises to €60 billion per year in the European Union (EU), of which 33% is related to direct health care costs, 29% to productivity losses (20% because of mortality and 9% because of morbidity) and 38% to the informal care (Nichols et al, 2012).

Conventional medicine is mainly focused on clinical measures and functional outcomes; however, morbidity and mortality rates do not reflect all aspects of health. Over the years, patients' self-perceived emotional, social and physical well-being has gained attention, especially in long-term chronic conditions, when full recovery is quite unlikely. Many patients consider the quality of the additional life years gained equally important as the length of life (Thompson et al, 2003). Due to pain, physical and social restrictions, anxiety or depression, cardiovascular patients are particularly vulnerable to have an impaired self-perceived quality of life (Mols et al, 2009; Schweikert et al, 2009; Thompson et al, 2003; Xie et al, 2008). The goal of today's medicine is therefore not merely to simply extend a person's life expectancy, but also to ensure a sufficiently high long-term health-related quality of life (HRQoL) (Dunning et al, 2008; Oldridge et al, 2005). Consequently, HRQoL assessment is increasingly being used; initially for scientific research purposes only, but later on also in daily clinical practice.

1.1 CORONARY HEART DISEASE AND ITS PREVENTION

CHD is a disease of the arteries and vessels supplying blood and nutrients to the heart muscle. Due to plaque build-up over the years, the arteries narrow and harden (i.e. atherosclerosis), hence preventing an adequate blood flow (World Health Organisation, 2004). Such a blockage can lead to myocardial ischemia, which is characterized by angina or chest pain. When left untreated, this may evolve into an acute myocardial infarction (AMI), also known as a heart attack. Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Grafting (CABG) are frequently used interventions proven to be effective in reducing the subsequent risk for a recurrent coronary event (Bravata et al, 2007).

About 22% females and 20% males die from the illness (1.8 million deaths across Europe per year). Standardized case fatality rates vary greatly between countries, but on average the 30-day case fatality after admission for an AMI amounts to 4.8%. During the latest decade, the average hospital discharge rate for CHD lies around 800 per 100,000 discharges across Europe and about 10% of all Disability Adjusted Life Years (DALYs) are caused by CHD (Nichols et al, 2012). Between 1995 and 2007 a major increase in medication use has been observed in CHD patients. The use of antiplatelet therapy increased from 81% to 93%, the use of blood pressure lowering drugs increased from 84% to 97%; the use of Beta-blockers increased from 56% to 86%, the used of lipid lowering drugs increased from 32% to 89%, and statin use increased from 18% to 87% (Kotseva et al, 2009a).

Over the years several CHD risk factors have been described. In this thesis, we distinguish four risk factor categories (Gaziano et al, 2001). First there are the non-modifiable predisposing risk factors such as age, gender, family history, genetic predisposition, educational level and socio-economic status. Secondly, metabolic risk factors exist such as elevated cholesterol, high blood pressure (BP), diabetes, overweight and obesity. Thirdly, behavioural risk factors exist, such as smoking, lack of physical activity, an unhealthy diet and excessive alcohol intake. And finally psychosocial factors such as stress, anxiety and depression as well as an impaired self-perceived health status and general health perceptions are considered CHD risk factors (Berry et al, 2012; Buttar et al, 2005; DeSalvo et al, 2006; World Health Organisation, 2002; World Health Organisation, 2004).

According to the EUROBAROMETER survey, 29% of citizens across the EU are smokers (Eurobarometer, 2010). Over 30% of Europeans citizens do not perform any kind of recreational or leisure time physical activity (Eurobarometer, 2006) and the national mean body mass index (BMI) levels for both men and women across Europe vary between around 24 and 28 kg/m^2, whereas the optimal value for the health of a population is 21 kg/m^2 (Nichols et al, 2012).

A survey in 4366 asymptomatic high risk patients (patients on antihypertensive and/or lipid-lowering and/or anti-diabetes treatments, but with no history of a coronary or other atherosclerotic disease) across the general practices of 12 European countries, revealed that 16.9% of patients were smokers, 43.5% had a BMI ≥30 kg/m^2, 70.8% had a BP ≥140/ 90mmHg (≥130/80 in people with diabetes mellitus), 66.4% had a total cholesterol (TC) ≥5.0mmol/l (≥4.5mmol/l in people with diabetes) and 30.2% reported a history of diabetes (Kotseva et al, 2010).

A sample of CHD patients revealed that 17% of patients were smokers, 35% were obese and 52% centrally obese, 56% had a BP ≥140/90 mmHg (≥130/80 in people with diabetes mellitus), 51% had a serum TC ≥4.5 mmol/l and 25% reported a history of diabetes (Kotseva et al, 2009b).

A profound study by Yusuf et al (2004), indicated that smoking, hypercholesterolemia, hypertension, diabetes and obesity are responsible for 80% of the risk for a first acute AMI. Hence, adequate lifestyle changes are crucial in order to decrease CHD related morbidity and mortality rates. Several guidelines on cardiovascular prevention emphasize the importance of adopting a healthier lifestyle in order to prevent coronary events both in CHD patients as well as in high risk patients. In 1994, the European Society of Cardiology (ESC) has published formal recommendations on the prevention of CHD in clinical practice aiming to summarise – from a clinical point of view – the most important issues in CHD prevention based on the available evidence, in order to help physicians in their everyday clinical medical decision making (Pyorala et al, 1994). Regular updates of the guidelines have been published since; the latest version was made available in 2012 (Perk et al, 2012).

Tobacco use is estimated to be responsible for nearly 10% of cardiovascular diseases (World Health Organisation et al, 2011), therefore, smoking cessation aid should be offered and second-hand or passive smoking should be avoided (Perk et al, 2012; World Health Organisation et al, 2011). Furthermore, attention should be given to dietary habits, since an unhealthy diet, consisting of a high fat and salt intake and a low fruit, vegetables and fish intake is associated with an increased CHD risk (World Health Organisation et al, 2011). Healthy dietary habits should be adopted by reducing saturated fatty acids intake (<10% of total energy intake) through replacement by polyunsaturated fatty acids intake, by avoiding trans unsaturated fatty acids intake, by reducing salt intake (<5g/day), by increasing fibre intake (30-45g/day), fruit and vegetable intake (200g/day each), and fish intake (2x/week), and by limiting alcohol intake (2 glasses/day for men, and 1 glass/day for women) (Perk et al, 2012). Currently, more than 60% of people worldwide do not meet the physical activity targets (World Health Organisation, 2004). Healthy adults are advised to spend 2.5 to 5 hours/week of moderate intensity physical activity, or 1 to 2.5 hours/week of vigorous intensity physical activity (Perk et al, 2012). An imbalance between energy intake and energy expenditure can lead to overweight (BMI ≥25kg/m² and <30kg/m²) and obesity (BMI ≥30kg/m²), resulting in adverse metabolic effects on BP, cholesterol, triglycerides and insulin resistance (World Health Organisation et al, 2011). In addition, waist circumference targets are set at <94 cm and <80 cm in men and women respectively. Overweight and obese persons should be recommended to lose weight in order to achieve a BMI <25kg/m² (Perk et al, 2012). Treatment of risk factors should further include treatment of hypertension since, in terms of attributable deaths, a raised BP is the leading cardiovascular risk factor globally (World Health Organisation et al, 2011). Prevention should focus on behavioural strategies and antihypertensive drug treatment if necessary, in order to lower the BP to <140/90mmHg (Perk et al, 2012). Diabetes is associated with a 2 to 3 fold increased risk for cardiovascular disease (CVD) (World Health Organisation et al, 2011). Hence patients with diabetes should be treated in order to reduce the glycated haemoglobin (HbA1c) level <7.0%; furthermore their BP should be lowered to <140/80mmHg and the use of statins is recommended in all diabetes patients. Indeed, cholesterol is another major risk factor. A third of CHD is caused by elevated cholesterol levels (World Health Organisation et al, 2011). In coronary patients, the recommended low density lipoprotein cholesterol (LDL-C) target is <1.8mmol/L or a ≥50% LDL-C reduction when the target level cannot be reached (Perk et al, 2012).

Moreover, coronary patients are at higher risk to develop both depressive and anxious feelings as well as to suffer from impaired HRQoL outcomes, due to pain, physical and social restrictions. Depression, psychosocial stress, emotional but also physical well-being are in turn independent predictors of worse CHD outcomes (World Health Organisation, 2004; Spertus et al, 2002; Schenkeveld et al, 2010; Rumsfeld et al, 1999; Pedersen et al, 2007; Pedersen et al, 2011; Kivimaki et al, 2012). Hence, tackling patients' depressive and anxious feelings as well as improving their HRQoL is of utmost importance. Knowledge on how to improve HRQoL outcomes is scarce, although some suggest that the effect of changing lifestyle behaviours is twofold; not only will it have a direct impact on obesity, cholesterol, BP and blood glucose but also an indirect impact by influencing a individual's HRQoL (Bize et al, 2007; Piper et al, 2012; Sarna et al, 2008; Sevinc et al, 2010).

The IMPACT model, developed by Capewell and colleagues revealed that between 1981 and 2000, CHD mortality rates in England and Wales decreased by 62% in men and 45% in women. About 42% of this decrease could be attributed to treatments in individuals. Secondary prevention accounted for an 11% reduction, heart failure treatment for 12%, AMI treatment for 8%, hypertension treatment for 3% and angina treatment for 9%. Population risk reductions make up 58% of the mortality decrease. Smoking cessation accounted for 48%; blood pressure lowering for 9.5%; and cholesterol lowering 9.5%; deprivation decrease for 3%. Adverse trends were seen for physical activity, obesity and diabetes, responsible for a 4.4%, 3.5% and 4.8% increase in CHD mortality respectively (Unal et al, 2004).

1.2 HEALTH-RELATED QUALITY OF LIFE: FROM ORIGIN TO MEASUREMENT

The interest in the concept ‘quality of life’ dates back to the ancient Greek era. In their moral theories Socrates, Plato and Aristotle defined ‘happiness’ as an important goal of action. They wondered how one should live to be happy. In his Nicomachean Ethics, Aristotle explored the concept *Eudaimonia*, which can be translated as ‘the good life’, ‘well-being’ or ‘happiness’. And although modern philosophers are still discussing about the correct meaning and translation of the concept, there is agreement about the theory of Eudemonism being closely related to a person’s self-perceived quality of life. What Aristotle considered as being the ‘highest of all goods’ in human beings, is still believed to be the ultimate goal in every person’s life. The term quality of life is frequently being used in social science. However, in order to differentiate between a person’s overall happiness or quality of life and his/her health-related well-being the concept HRQoL has been introduced.

The interest in patients’ self-perceived health-related well-being was already reflected shortly after World War II in the preamble of the constitution of the WHO. Within this preamble (1946), health was defined as *"a state of complete physical, mental, and social well-being; not merely the absence of disease or infirmity”*, including mental and social well-being as a substantive part of health (World Health Organisation, 1948). However, it was not until the mid-70’s that HRQoL was included as a keyword in the Index Medicus (Snoek, 2000). Ever since, a large number of definitions explaining the concept have emerged. A few of them are listed below:

According to Wegner and Furberg (1990) (Spilker, 1990) HRQoL can be defined as:

> *“Those attributes valued by patients, including: their resultant comfort or sense of well-being; the extent to which they were able to maintain reasonable physical, emotional and intellectual function; and the degree to which they retain their ability to participate in valued activities within the family, in the workplace and in the community”*

According to Revicki (2000) (Revicki et al, 2000) HRQoL can be defined as:

> *“The subjective assessment of the impact of disease and treatment across the physical, psychological, social and somatic domains of functioning and well-being”*

And the WHO (World Health Organisation, 1995) defines HRQoL as :

> *“The individual perception of their position in life in the context of their culture and value systems in which they live and in relation to their personal goals, expectations, standards and concerns”*

Clearly HRQoL is highly individual and means different things to different people, depending on demographic, psychological, socioeconomic and other characteristics (Carr et al, 2001). Each person has his/her own interpretation of the concept, driven by his/her own expectations, hopes and ambitions (Carr et al, 2001). As suggested by Schipper et al (1996), HRQoL measurement is subjective in two ways. First of all, HRQoL dimensions are hardly physically measurable and secondly the patient’s view on a disease is as important as the disease itself.

In any case HRQoL should be used in addition to and by no means replace objective disease outcome measures (Higginson et al, 2001; Duenas et al, 2012). Despite the extensive use of the concept, consensus is lacking on the definition of HRQoL. The term is used to describe a variety of concepts, such as functioning, health status, perceptions, life conditions, behaviour, happiness, lifestyle, symptoms etc. (Simko et al, 1999), therefore HRQol is sometimes referred to as an umbrella term (Feinstein et al, 1987). However, in essence HRQoL captures a person's self-perceived impact of a medical condition, its symptoms and its treatment (Schipper et al, 1996). In this context, not only the patients' perceived level of satisfaction with their physical functioning, but also with their emotional and social functioning should be assessed (Moons et al, 2004). In the literature the term HRQoL is frequently used to refer to perceived health status. Although these concept are often used interchangeably, there are subtle differences between the terms, with health status actually being a determinant for HRQoL. A review by Smith et al (1999), revealed that from a patient perspective health status and HRQoL are two distinct constructs. Whereas, compared to physical functioning, mental health has the greatest impact on HRQoL, the reverse is true for perceived health status, with physical functioning being the main determinant.

The revised Wilson and Cleary Model for HRQoL provides a theoretical background of the different concepts constituting HRQoL (figure 1) (Ferrans et al, 2005).

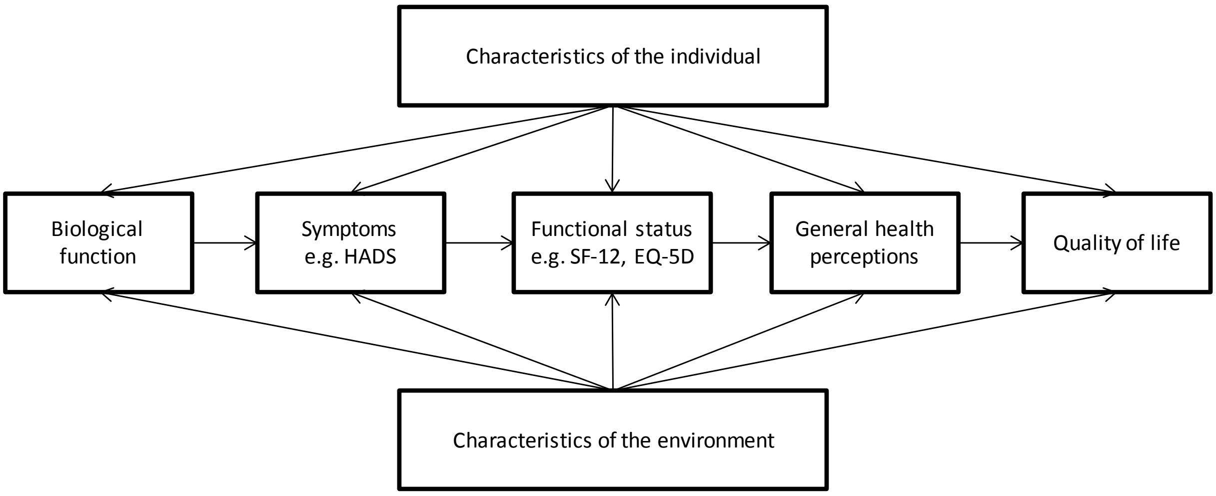


Figure 1: Revised Wilson and Cleary model for Health-related Quality of life. Ferrans, et al. (2005). Adapted from Wilson & Cleary (1995). Copyright JAMA.

To start, intrapersonal factors, interpersonal factors, institutional factors, community factors and public policy are linked with all components determining HRQoL. Secondly, five types of measures of patient outcomes can be distinguished. Biological function encompasses molecular, cellular, and whole organ level processes and can be assessed by laboratory tests, physical assessment, and medical diagnoses. Biological functions are directly linked with symptoms, the second patient outcome. Symptoms can be defined as *"a patient's perception of an abnormal physical, emotional or cognitive state".* Instruments to measure symptoms can be divided into global measures (e.g. Symptom Impact Inventory (Miller et al, 2001)); condition specific measures (e.g. Unstable Angina Symptom Questionnaire (DeVon & Zerwic, 2003)); and symptom specific measures (e.g. the Hospital Anxiety and Depression scale

(HADS) (Zigmond et al, 1983)). Functional status is being defined as *"the ability to perform tasks in multiple domains such as physical function, social function, role function and psychological function"*. Both objective (e.g. the Shuttle Walk Test where the patients is asked to walk up and down over a 10 meters distance (= a shuttle) with an audio signal used to guide the walking speed of the patient (Singh et al, 1992)) and subjective (patient perceived health status) instruments can be used. The most often used generic self-perceived health status instruments are the 36-item Short Form health survey (SF-36), the 12-item Short Form health survey (SF-12) (Ware et al, 2002; Ware et al, 1996) and the EuroQol 5 dimensions (EQ-5D) (The EuroQol Group, 1990; The EuroQol Group's International Task Force on Self-Reported Health, 2004). Widely used disease specific instruments in coronary patients are the Seattle Angina Questionnaire (SAQ) (Spertus et al, 1995) and the Myocardial Infarction Dimensional Assessment Scale (MIDAS) (Thompson et al, 2002). Next we have the general health perception, which should be measured with a single global question, asking people to rate their health ranging from poor to excellent. These can be standalone measures with one single item or they can be part of a more comprehensive measure, with 1 item assessing the general health perception (e.g SF-36, SF-12). The final component of the model captures the subjective well-being of how happy or satisfied someone is with his/her (health-related) life as a whole (Ferrans et al, 2005). Examples of such instruments for use in coronary patients are the MacNew Heart Disease Health-related Quality of Life Questionnaire for heart failure, coronary disease and myocardial infarction (Valenti et al, 1996; Lim et al, 1993), and more recently HeartQoL for patients with angina, MI, or ischemic heart failure (Oldridge et al, 2005). The above described patient outcome measures are dynamic and can change over time not only due to the changes in a patient's physical condition but also because of changes inherent in life, such as ageing.

As mentioned, both generic measures as well as disease specific tools exist. The former are applicable across a wide range of different patient groups and populations focusing on more general issues. Hence, comparison of the outcomes with other patient groups or with the general population is possible, allowing to assess the particular impact of a given condition. They have the potential limitation however, not to capture certain issues associated with an illness. Disease specific measures on the contrary, serve for specific use in a certain disease area. They are more appropriate to capture changes associated with the disease (Swenson et al, 2000) but do not allow comparison with the general population, making interpretation rather difficult.

Within the context of this PhD research, we made use of three instruments, which were included in the EUROASPIRE III (EURopean Action on Secondary Prevention through Intervention to Reduce Events) protocol, as further discussed in chapter 2.

The EQ-5D instrument, developed by the EuroQol group in 1990, is a standardized instrument to measure one's self-perceived health status (Bowling, 2005; Ferrans et al, 2005). It can be used across different conditions, treatments and settings. Designed for self-completion it is applicable for use in postal surveys, in clinics, and in face-to-face interviews. Within the current study we have used the EQ-5D-3L (3 level) version. The instrument is composed of two parts: the EQ-5D descriptive system and the EQ visual analogue scale (EQ-

VAS). The former includes five questions covering five different dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each question has 3 response categories: no problems, some problems, and severe problems, allowing the respondent to rate their own health. For the mobility dimension for example the respondent is asked to place a tick next to one of the following options: 'I have no problems in walking about'; 'I have some problems in walking about'; 'I am confined to bed'. The outcome of the descriptive system can be represented as a health state. A respondent for example having no problems with mobility, some problems with self-care, some problems with usual activities, having no pain or discomfort and being extremely anxious or depressed will have '12213' as health state, from which a single EQ-$5D_{index}$ score, also known as a utility (see below), can be calculated (Dolan, 1997; Rabin et al, 2011; Rabin et al, 2001). An index score of 1 represents perfect health, a value of 0 represents death, and a value below 0 represents a health state perceived worse than death. The second part of the instrument, the EQ-VAS is a 20-cm vertical scale, ranging between 0 (worst imaginable health state) and 100 (best imaginable health state) on which the respondent is asked to indicate how good or bad his or her health is today.

The second measure used is the SF-12. Originally developed in 1994, the SF-12 is a downsized version of the SF-36, and is intended to measure functional health and well-being from a patient perspective. Similar to the EQ-5D instrument, the SF-12 tool is classified as a broader health measure (Bowling, 2005). The SF-12 is available in a standard (4-week recall period) and an acute (1-week recall period) version. In the current study the second version of the standard SF-12 is being used (the SF-12v2, hereafter referred to as SF-12). The instrument consists of 12 questions, with 3 to 5 response levels each, covering 8 health domains: physical functioning (PF - two questions), role physical (SF-12/RP - two questions), bodily pain (SF-12/BP - one question), general health (SF-12/GH - one question), vitality (SF-12/VT - one question), social functioning (SF-12/SF - one question), role-emotional (SF-12/RE - two questions), and mental health (SF-12/MH - two questions). From the different responses on the individual questions, a single score between 0 and 100 can be calculated for each dimension, with a higher score indicating a better health status (Ware et al, 2002). Using a scoring algorithm, two component measures can be calculated from these scales, a Physical Component Summary (PCS-12) score and a Mental Component Summary (MCS-12) score, represented by a value ranging between 0 and 100 (Ware et al, 2002). The scores allow assessment of both physical and mental functioning respectively. In the general population, on average an overall mean theoretical score of 50 (SD=10) is expected on both measures. Lower and higher scores indicate worse and better health outcomes respectively. In addition, an algorithm was developed in order to calculate a utility score based on the SF-12 outcomes (Brazier et al, 2004b).

Finally, the HADS was used. This instrument, developed in 1983, was initially intended for use in a hospital setting, but has also been proven to be reliable and valid in a primary care setting (Zigmond et al, 1983; Bowling, 2005). This scale is useful for measuring psychological well-being (Bowling, 2005). The instrument gives information about possible or probable anxiety or depression, but it is not appropriate for clinical depression screening because, unlike the Beck Depression Inventory (BDI) (Beck et al, 1996) or the Patient Health

Questionnaire (PHQ), this instrument is not based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. The scale contains 7 items related to anxiety and 7 to depression, each with a 4-point response scale. The questions cover the following issues: feeling tense, restless or relaxed; enjoying things, laugh and feeling cheerful; frightened feelings, feelings of panic and worrying; feeling slowed down and loss of interest in appearance. Item scores can be added to obtain the summary scores on anxiety (HADS-A) and depression (HADS-D) separately. Scores range from 0 to 21 with lower scores representing less anxious or depressive feelings respectively. A score below 8 can be considered as being in the normal range, a score between 8 and 10 suggests a possible depression or anxiety disorder a score greater than or equal to 11 indicates a probable depression or anxiety disorder.

1.3 HEALTH-RELATED QUALITY OF LIFE AND HEART DISEASE

As mentioned above, CHD is associated with a substantial mental and physical burden (Ski et al, 2010). Depression and anxiety are highly prevalent in coronary patients. A recent review by Celano et al (2011) concluded that 31% to 45% of coronary patients suffer from depressive feelings. According to Todaro et al (2007) 36% of CHD patients suffer from at least one anxiety disorder whereas Bankier et al (2004) mention an anxiety prevalence of 24% among stable CHD patients. Similar results were found in the EUROASPIRE III (EUROpean Action on Secondary and Primary Prevention through Intervention to Reduce Events) survey with a prevalence of depressed patients (HADS-D ≥8) amounting to 21% in men and 32% in women, and a prevalence of anxiety (HADS-A ≥8) reaching 27% in men and 44% in women (Pajak et al, 2013). Likewise, self-perceived health status is significantly impaired in CHD patients. A study performed by Xie et al. (2008) in the United States, indicated significant differences in self-perceived health status between CHD patients and the general population, particularly on general and physical health. Decrements in health status seemed to be larger in younger persons and in women. The MONICA/KORA registry in Germany revealed similar results, with MI survivors being at higher risk for reporting problems with regard to pain/discomfort, usual activities, and anxiety/depression (Schweikert et al, 2009).

These are important findings since impaired health status, depression and anxiety are known risk factors for cardiovascular disease, as well as independent predictors of mortality and cardiac outcome in coronary patients. Several studies have indicated clinical depression as an independent risk factor for adverse cardiac outcome and mortality, both in the general population as well as in CHD patients. Within the general population, the Health Study of Nord-Trøndelag County (HUNT-2) has demonstrated a higher risk for both CHD (1.3-fold increased risk) as well as mortality (1.5-fold increased risk) in depressed persons (Mykletun et al, 2009, Gustad et al, 2013). According to Luukinen et al (2003) depression is associated with a 2.7-fold higher risk of sudden cardiac death and a 1.7-fold higher risk for all-cause mortality. The meta-analysis by Van Melle et al (2004) has shown a 2- to 2.5-fold increased risk of impaired cardiovascular outcome in post MI depression. Depression was significantly associated with all-cause and cardiac mortality and new cardiovascular events (van Melle et al, 2004). According to the meta-analysis performed by Barth et al (2004), the 2-year overall mortality risk of depressed CHD patients was two times higher than in non-depressed CHD patients. Similar results were found regarding long-term prognosis. A recent study by Nabi et al. (2010) investigating 5936 middle-aged men and women from the British Whitehall II study showed a additive interaction between depressive symptoms and CHD with regard to mortality. According to the most recent meta-analysis performed by Meijer et al (2011) post-MI depression was associated with a 1.6- to 2.7-fold increased two-year risk of impaired outcomes.

Similar results were found with regard to anxiety. According to a meta-analysis performed by Roest et al. (2010a) in healthy persons, anxiety was significantly associated with a greater risk for both CHD (1.3-fold increased risk) and cardiac death (1.5-fold increased risk). A meta-analysis in coronary patients showed that post-MI anxiety was associated with a 36% increased risk of adverse cardiac outcomes, a 47% increased risk of all-cause mortality, a 23% increased risk of cardiac mortality and a 71% increased risk of new cardiac events (Roest et al, 2010b). Freasure-Smith (1995) found a 1-year OR of 2.52 for a recurrent cardiac event in anxious post MI patients.

Likewise, functional status, general health perception and HRQoL measures have been shown to be independent predictors of cardiovascular outcome. Physical health status assessed during hospitalization for acute coronary syndrome (ACS) predicted mortality 12 months later (Thombs et al, 2008); Seattle Angina Questionnaire (SAQ) scores were independently associated with 1-year mortality and ACS in coronary patients (Spertus et al, 2002) and Kato et al. (2011) found that the outcome of the Minnesota Living with Heart Failure (MLHF) questionnaire was an independent predictor of cardiac events and death. Furthermore Pedersen (2007) concluded that poor MacNew outcomes were a predictor of early death/MI but not late death/MI. Likewise, Agewall (2012) stated that a low self-estimated HRQoL was associated with poor outcome after MI. Even a single question assessing the general health perceptions was a significant predictor of mortality (Burstrom et al, 2001; DeSalvo et al, 2006). According to De Salvo (2006), compared to patients in excellent health, patients with a poor self-rated health had a 2-fold greater mortality.

Research on the link between physical and mental well-being and cardiovascular outcome is still on-going. Two main directions concerning the link can be distinguished. First, impaired patient reported outcomes can cause a coronary event, and secondly CHD patients are more prone to develop depressive and anxious feelings and to have impaired functional status or HRQoL outcomes. Several possible mechanisms, explaining the link have been proposed. First of all CHD risk factors such as smoking, high cholesterol, hypertension, diabetes and obesity tend to cluster in depressed patients putting them at higher risk for developing a cardiac event (Joynt et al, 2003; Pozuelo et al, 2009). Moreover, clinical depression can increase noncompliance with medical treatment and lifestyle changes (Joynt et al, 2003; Pozuelo et al, 2009). Due to the outlook of hopelessness, depressed patients often have no confidence in the benefits of CHD treatment, furthermore they also seem to be more sensitive to adverse events and are thus more likely to discontinue medication use (Gehi et al, 2005). According to Kurdyak (2011), self-reported cardiac functional health status may serve as a key causal pathway explaining the association between depression and mortality after AMI with functional capacity, in particular physical inactivity being a predictor of mortality.

In addition to these behavioural patterns, some physiologic changes are observed in depressive patients. We shortly address the main pathways. Stress induces a decreased parasympathetic and increased sympathetic nervous system activity (autonomic nervous system dysfunction). This imbalance is associated with decreased heart rate variability, which is a risk factor for arrhythmia and sudden cardiac death. Furthermore, hyperactivity of hypothalamus pituitary-adrenal axis is seen in depressed patients leading to increased cortisol levels. Although this is an important beneficial effect in response to stress, chronic stress will lead to chronically elevated cortisol levels increasing the risk of CVD trough adverse metabolic effects (visceral obesity, insulin resistance, endothelial dysfunction, increased LDL-cholesterol and triglyceride levels and increased intake of comfort food). On the other hand, sympathoadrenal activation -often seen in depressed patients- can lead to increased levels of catecholamines, causing vasoconstriction, a rapid heart rate, and platelet activation. The activation of platelets (platelet factor IV and beta-thromboglobulin) can induce vascular damage and thrombosis. Finally, an increase in inflammatory markers is observed in depressed patients which is associated with atherosclerosis and hence CHD (Celano et al, 2011; Joynt et al, 2003; Pozuelo et al, 2009).

1.4 RELEVANCE OF HEALTH-RELATED QUALITY OF LIFE

As mentioned above, the use of patient reported outcome measures has increased over the years. Such assessment is useful in evaluating a medical treatment in clinical research, but can just as easily be used in daily clinical practice to identify health needs or to measure disease impact. Hence, by monitoring changes and outcomes in self-reported health among patients, treatment plans can be adjusted where needed (Mayou et al, 1993). The more objective clinical outcomes are not always a reflection of how a disease, its symptoms and treatment are experienced by the patient (Guyatt et al, 1993). Pain for example is difficult to capture with the conventional measures. In addition, great differences have been observed in health status outcomes between patients with the same clinical profile, stressing the importance of assessing patient’s self-perceived health in order to adjust treatment accordingly. Health status and HRQoL information can also be helpful for audit purposes, and for assessing the quality of delivered health care. Finally, these measures can also be used in health policy decision making (Guyatt et al, 1993; Mayou et al, 1993). Scarce health care resources have led to the development of health economic evaluations. These are used as decision making tool in order to maximize health benefits with the available financial means. Health benefits are often expressed as a combination of patients’ prolongation of life and their self-perceived health status during that time period. Health economic analyses might be particular important to assess the cost-effectiveness ratio of CHD prevention. As discussed above, CHD is a major cause of health care expenses and impaired health status and HRQoL outcomes. CHD prevention can help to reduce the morbidity and mortality burden associated with the illness. Health economic analyses are useful in prioritizing policy goals and allocating resources to the most appropriate intervention.

1.5 AIMS AND SCOPE OF THIS STUDY

The general aim of this thesis was to focus on functional status and psychological well-being using a large database of stable coronary patients, the EUROASPIRE III survey. Figure 2 gives a conceptual overview of our research questions. Despite the conceptual difference between health status and HRQoL as discussed above, we will talk about HRQoL and psychological distress in the remainder of this thesis to indicate the three measures (EQ-5D, SF-12, HADS) used.

To start, we investigated whether the three instruments (EQ-5D, SF-12 and HADS) used were valid and reliable within the EUROASPIRE III sample (chapter 3). Some studies have already performed psychometric analyses in CHD patients, however often based on smaller samples, or samples of acute CHD patients. Furthermore, the interpretation of the outcomes is difficult, if not impossible in the absence of reference values from the general population, hence, EQ-5D results from the EUROASPIRE III sample were compared with published country-specific normative values (chapter 4).

The primary purpose of this thesis however, was to investigate the association between CHD and HRQoL/psychological distress, and to determine the factors possibly responsible for HRQoL/psychological distress impairments. Prior studies have found an association between impaired HRQoL, anxiety, depression and worse long-term cardiovascular outcomes (Thombs et al, 2008; Spertus et al, 2002; Kurdyak et al, 2011). Hence, investigating the association between cardiovascular risk profiles in CHD patients and their HRQoL/psychological distress, as well as investigating the relationship between risk factor level awareness and HRQoL/psychological distress can be important both for patients and families, for health-care providers, as well as for decision makers in order to tailor patient treatment and policy goals accordingly.

First of all, we hypothesised that patient characteristics and their cardiovascular risk profile (chapter 5) would be associated with their HRQoL outcomes. We investigated the influence of geographical location on HRQoL in CHD patients. Furthermore we assessed whether there was a significant association between predisposing risk factors (age, gender, educational level and cardiovascular history) and HRQoL. Likewise the association with metabolic (BP, TC, LDL-C, fasting glucose and HbA1c) and behavioural risk factors (smoking, physical activity and healthy diet) was investigated. We hypothesized that poor cardiovascular risk profiles would be associated with worse HRQoL outcomes in coronary patients. Within the general population, patient characteristics are significantly associated with HRQoL outcomes, with increasing age, female gender, low education, diabetes, obesity and cardiovascular events being associated with worse outcomes (Franco et al, 2012; Martinelli et al, 2008). Similarly, smoking and physical inactivity are associated with impaired HRQoL results (Piper et al, 2012; Bize et al, 2007). With regard to metabolic risk factors, a significant association between HRQoL and hypertension has been reported in coronary patients, whereas no association was found with hypercholesterolemia (Soini et al, 2010; Sevinc et al, 2010; Herlitz et al, 2005).

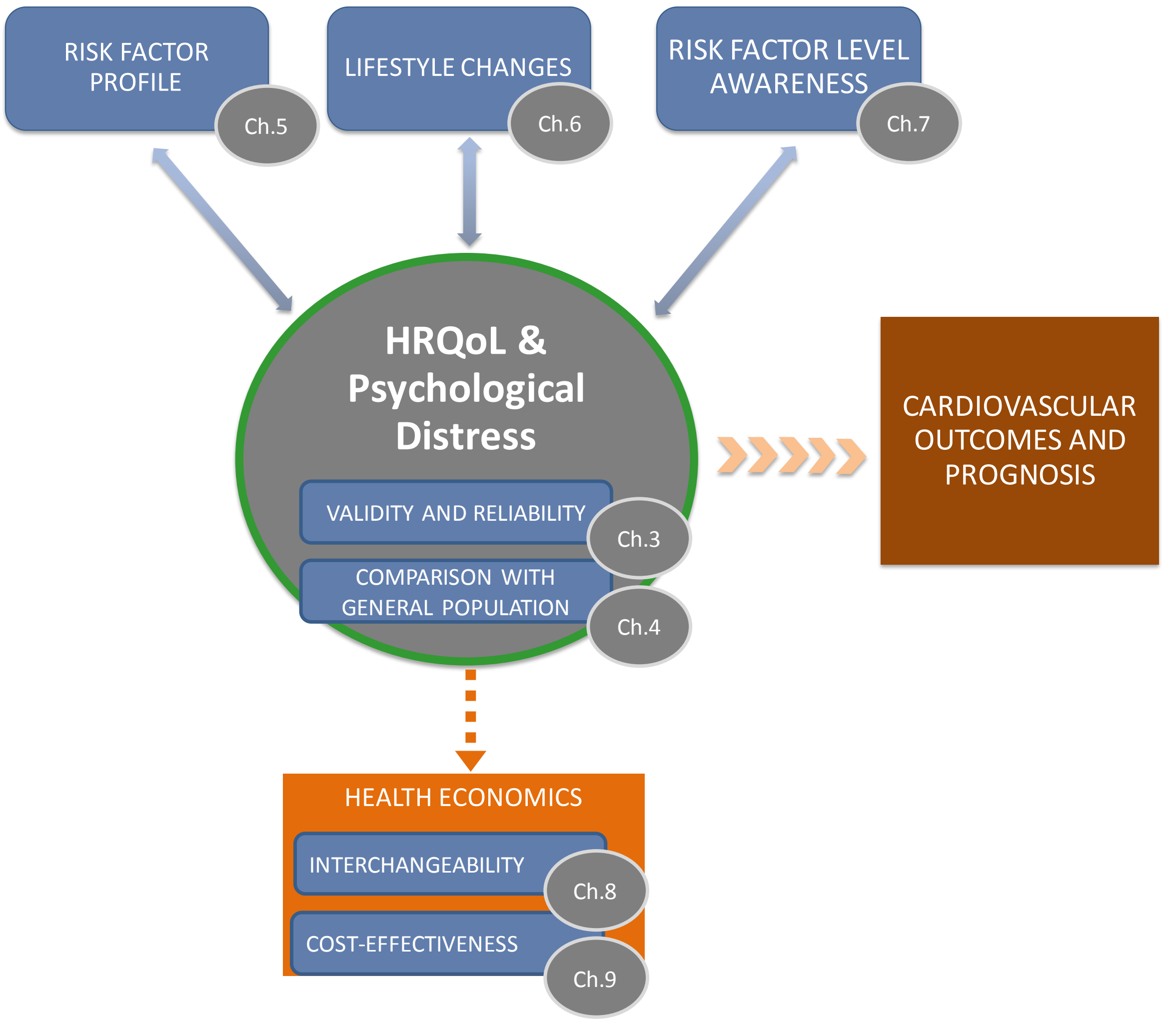


Figure 2: Research questions addressed within this thesis. The blue rounded squares indicate the investigated topics. The pink arrow shows what is already known from the literature. The dotted orange line indicates how HRQoL and psychological distress can be used in practice.

Additionally, we investigated the association with behavioural changes. Lifestyle changes are directly related to risk factors and cardiovascular prognosis (Yusuf et al, 2004). We hypothesized that coronary patients who have not made an attempt to change their behaviour in order to adopt a healthier lifestyle would also have worse HRQoL/psychological distress outcomes (chapter 6). Indeed, in the general population smoking cessation is associated with improved HRQoL/psychological distress outcomes. Piper et al (2012), has found a fast improvement after cessation that sustained over at least 3 years, whereas Within the Nurses' Health Study, HRQoL scores improved gradually with longer time since quitting (Sarna et al, 2008). Likewise improvements in physical activity seem to be associated with better HRQoL outcomes (Martin et al, 2009; Bize et al, 2007). In addition to the studies performed in the general population, some studies report on these findings in coronary patients, however, the sample size is often limited and geographical areas are often restricted to a single region or country.

Moreover, we hypothesized that risk factor awareness in CHD patients would be associated with improved HRQoL/psychological distress outcomes (chapter 7). We investigated the association between risk factor level awareness in patients and their HRQoL/psychological distress, and searched for different pathways possibly explaining the association. This issue has not yet been addressed previously in CHD patients. In the general population hypertensive patients who were aware of their elevated BP had worse HRQoL/psychological distress outcomes, compared to those persons unaware of their hypertension. Furthermore, a higher sick leave is reported in such patients (Mena-Martin et al, 2003).

Secondly, we investigated the interchangeability between two different HRQoL measures in our sample of coronary patients: the EQ-5D and the SF-12 (chapter 8). Both measures allow calculating a utility value, which can be used in health-economic evaluations. A recent study by Joore et al. (2010) reported remarkable differences in cost-effectiveness results, depending on the instrument used. Patients with mild health conditions had higher SF-6D scores, whereas patients with severe conditions had higher EQ-5D scores. This leads to better or worse cost-effectiveness outcomes, depending on the HRQoL instrument used. The incomparability of the results using different instruments poses a real threat on the usefulness and credibility of cost-effectiveness analyses. Within our knowledge, only one study reports on the comparison between EQ-5D utility values and SF-36 utility values in a sample of coronary patients (van Stel et al, 2006).

Finally, the usefulness of HRQoL as policy tool was tested. The individual EQ-5D utilities from the EUROASPIRE III sample were used to calculate the cost-effectiveness of optimal cardiovascular prevention in coronary patients. Whereas many studies already reported on the cost-effectiveness of single prevention strategies, none conducted an integrated tailor-made cost-effectiveness analysis on secondary cardiovascular prevention targeting different intervention strategies simultaneously, adapted to the current prevention status of patients (chapter 9).

In summary, the outline of the thesis is as follows:

- Chapter 1 gives an introduction regarding the research questions.
- Chapter 2 reports on the methodology used throughout the doctoral thesis.
- Chapter 3 investigates the psychometric properties of the EQ-5D, SF-12 and HADS instrument in order to assess the validity and reliability of these tools in stable coronary patients .
- Chapter 4 reports on the comparison in EQ-5D outcomes between coronary patients and the normative population.
- Chapter 5 examines the relationship between the cardiovascular profile of coronary patients and their EQ-5D and SF-12.
- Chapter 6 explores the relation between several self-reported lifestyle changes and EQ-5D, SF-12 and HADS outcomes in coronary patients.
- Chapter 7 investigates the association between risk factor level awareness among patients and their EQ-5D, SF-12 and HADS.
- Chapter 8 assesses the inter-changeability between EQ-5D and SF-12 utility outcomes.

- In chapter 9, we assessed the cost-effectiveness of secondary prevention in coronary patients.
- The general discussion presented in chapter 10 provides a brief summary of the main findings, and subsequently proceeds with a profound discussion, evaluating the possible consequences for clinical practice.

Previous research has reported on the significant association between HRQoL/psychological distress and cardiovascular outcome. Within this PhD thesis, we further investigated the association between risk factor profile, lifestyle changes and risk factor level awareness and HRQoL/psychological distress in CHD patients. Furthermore some theoretical concepts were investigated: validity and reliability of the instruments, and comparison of HRQoL/psychological distress outcomes between CHD patients and the general population. Finally, the usefulness of HRQoL instruments in decision making was investigated. First, by analysing the interchangeability between instruments and secondly, by performing a cost-effectiveness study of secondary prevention in the EUROASPIRE sample.

Chapter 2.
General methodology

2.1 EUROASPIRE III: STUDY DESIGN

Analyses included in this thesis are based on EUROASPIRE III (European Action on Secondary and Primary Prevention Through Intervention to Reduce Events) data. In order to evaluate the guideline implementation in daily practice, the European Society of Cardiology (ESC) has carried out several surveys during the latest decades. The first EUROASPIRE survey, conducted in 1995-1996 was based on a previously conducted survey in the UK (1995-1996), the ASPIRE (Action on Secondary Prevention through Intervention to reduce Events) survey (Bowker et al, 1996). EUROASPIRE I was carried out in 21 centres across nine European countries (Czech Republic, Finland, France, Germany, Hungary, Italy, the Netherlands, Slovenia and Spain). The purpose of EUROASPIRE I, was to assess whether the guidelines published in 1994 on prevention of Coronary Heart Disease (CHD) in clinical practice were being followed (EUROASPIRE Study Group, 1997; Pyorala et al, 1994). In 1998 an update of the guidelines was published, hence a second survey (1999-2000) was carried out, including 47 centres from 15 countries (EUROASPIRE I + Belgium, Greece, Ireland, Poland, Sweden, UK). The aim of EUROASPIRE II was to investigate whether clinical practice was changing to achieve the full potential benefits of CHD prevention (EUROASPIRE II Study Group, 2001; Wood et al, 1998).

Both surveys indicated a high prevalence of unhealthy lifestyles, modifiable risk factors and inadequate use of drug therapies, with great variation across countries. Moreover a substantial increase in obesity, and smoking among younger patients was seen when comparing both surveys (EUROASPIRE I and II Group, 2001). Hence, there was a need to raise the standard of preventive cardiology through more effective lifestyle interventions, control of other risk factors and appropriate use of cardio-protective medication.

After publishing the third revision of the ESC guidelines (De Backer et al, 2003) on cardiovascular prevention, EUROASPIRE III was conducted in 76 hospital centres across 22 countries (EUROASPIRE I + Belgium, Greece, Ireland, Poland, UK, Bulgaria, Croatia, Cyprus, Latvia, Lithuania, Romania, Russian Federation, Turkey). The participating countries represent different geographical areas of Europe with large differences in the organization of medical care and economic resources. Only those areas with a large defined population (> half a million of people) were selected. Within the selected area, at least one hospital offers interventional cardiology and cardiac surgery and one or more hospitals offer acute care for patients with acute myocardial infarction (AMI) and ischemia.

Patients, men or women, aged ≥18 years and <80 years at the time of identification, hospitalized for a first or recurrent clinical diagnosis or treatment were identified retrospectively from diagnostic registers, hospital discharge lists or other sources. Eligible patients were patient hospitalized for:

- an elective or emergency Coronary Artery Bypass Graft surgery (CABG), with the exclusion of surgery in the context of valve replacement, or when the primary diagnosis is not coronary artery disease
- an elective or emergency Percutaneous Coronary Intervention (PCI), both stents or other devices
- a first or recurrent acute myocardial infarction (AMI), ST elevation and Non ST elevation myocardial infarction (MI)
- an acute myocardial ischemia with no evidence of infarction (Troponin negative).

Patients were interviewed and examined at least 6 months and not later than 3 years after their index hospital admission. Data collection was organized using standardized methods and instruments. To capture information from the index hospital admission, trained research staff reviewed patients' medical records. Personal and demographic details as well as personal cardiovascular history, including stroke and transient ischaemic attack were extracted from the medical records. Furthermore information on other medical history, including hypertension, hyperlipidaemia and diabetes were obtained. Recorded measurements of blood pressure (BP), diabetes, lipids and smoking status and medication (generic name and total daily dose) were gathered if available.

At interview, structured questionnaires were used to collect personal and demographic details; personal cardiovascular history, including stroke, transient ischaemic attack and peripheral artery disease; other medical history, including hypertension, hyperlipidaemia and diabetes; family history of CHD for patients with premature disease (men <55 years and women <65 years); reported lifestyle and other risk factor management in relation to smoking, diet (including weight reduction), exercise, BP, lipids and glucose; medication (generic name and total daily dose); and level of education, school attendance and employment status.

The following measurements were performed: height (Seca MEASURING Stick model 220) and weight (SECA scale model 701) in light indoor clothes without shoes and calculated body mass index (BMI=weight/height^2); waist circumference (metal tape measures); BP (Omron M5-I automatic digital sphygmomanometer; Omron Healthcare, Japan) was measured twice in a sitting position on the right upper arm and the mean of the two measurements was used in the analyses; heart rate; venous blood for serum total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), triglycerides, calculated low density lipoprotein-cholesterol (LDL-C) according to the Friedewald formula (=TC - HDL-C - (triglycerides/5)), plasma glucose and glycated haemoglobin (HbA1c) in patients with diabetes; breath carbon monoxide (Smokerlyser Bedfont Scientific, Model Micro 4; Bedfont scientific Ltd., Rostester, Kent, UK); validated self-administered questionnaires: Hospital anxiety and depression scale (HADS) (Zigmond et al, 1983); EuroQoL-5D (EQ-5D) (Rabin et al, 2001), 12- item Short Form Health Survey (SF-12) (Ware et al, 2002) and international physical activity questionnaire (IPAQ) (IPAQ core group, 2005).

The risk factor targets used, were based on the third joint European guidelines on cardiovascular prevention (De Backer et al, 2003). A raised BP was defined as systolic blood pressure (SBP)/diastolic blood pressure (DBP) ≥140/90 mmHg (≥130/80 mmHg in patients with diabetes). An elevated TC was defined as TC ≥4.5 mmol/L. Raised LDL-C was defined as LDL-C ≥2.5 mmol/L and low high density lipoprotein-cholesterol (HDL-C) was defined as HDL-C <1/1.2 mmol/L for men/women. Raised fasting glucose was defined as fasting glucose ≥6.1 mmol/L among patients with self-reported diabetes and raised HbA1c as HbA1c ≥6.5% among patients with self-reported diabetes. Low physical activity was defined as less than 20 min moderate physical activity, three times a week. Central obesity was defined as waist circumference >102/88 cm (men/women). The World Health Organisation (WHO) classes were used for BMI classification: normal range was defined as BMI <24.9 kg/m^2; overweight was defined as BMI between 25 kg/m^2 and 29.9 kg/m^2, and obesity as BMI ≥30 kg/m^2. Smokers were those who reported to be a current smoker or who had a carbon monoxide in breath value exceeding 10 ppm at the time of the interview. IPAQ classes were calculated according to the guidelines for data processing and analysis (IPAQ core group, 2005). A low IPAQ score was defined as no activity or some activity reported but not enough to meet the other categories. A moderate IPAQ score was defined as 3 or more days of vigorous-intensity activity of at least 20 minutes per day, or 5 or more days of moderate intensity activity and/or walking of at least 30 minutes per day, or 5 or more days of any combination of walking, moderate-intensity, or vigorous-intensity activities achieving a minimum total physical activity of at least 600 MET-minutes/week. Metabolic equivalent (MET) is a common outcome measure used to express the energetic expenditure of different physical activities. A high IPAQ score was defined as vigorous-intensity activity on at least 3 days and accumulating at least 1500 MET-minutes/week or 7 or more days of any combination of walking, moderate- or vigorous- intensity activities accumulating at least 3000 MET-minutes/week. Patient were asked to describe their self-perceived physical activity level on the following scale: no physical activity; light physical activity; vigorous physical activity for 20 minutes, 2 or 3 times a week; or vigorous physical activity for 20 minutes >3 times a week.

Of the 13,935 patients eligible for the survey, 8966 (participation rate=73%) were interviewed and examined at least 6 months and not later than 3 years after their index hospital admission (median=1.24 year). Full information on EQ-5D and/or SF-12 and/or HADS was available for 8745 patients. The results of EUROASPIRE III revealed that a substantial proportion of CHD patients did not achieve the goals as put forward in the guidelines on cardiovascular prevention (Kotseva et al, 2009b). Overall, at the time of interview, the prevalence of smoking was 17%, although most smokers had received advice to quit smoking, 52% of patients smoking at the index event, were still smoking at the time of the interview. About 35% of CHD patients were obese and 53% of patients were centrally obese. In order to lose weight, 52% of obese patients had undertaken dietary actions and 38% had increased their physical activity level since their index event. However, more than 1 in 3 obese patients had not undertaken any action to lose weight. Furthermore, 56% of patients had an elevated BP, 51% had an elevated TC and 25% of patients reported having diabetes (Kotseva et al, 2009b). Great variations were seen across countries.

Comparison of the different EURASPIRE surveys, indicated a time trend, calling for a more effective lifestyle management of patients with CHD. Although the proportion of smokers remained the same, the proportion of female smokers <50 years had increased. Furthermore, the frequency of obesity as well as the frequency of self-reported diabetes has increased over the years. In contrast, the proportion of patients with a raised BP has remained similar, and the proportion of patients with an elevated TC has decreased substantially over the three surveys (Kotseva et al, 2009a).

2.2 HEALTH ECONOMIC EVALUATION

Health economic evaluations compare several treatment modalities designated to treat a certain disorder, e.g. comparing a new therapy with the current treatment method. Both costs as well as consequences are compared (cost per unit of health effect). The costs are often limited to direct medical costs, including the expenditures made by patients, health insurance or government. The consequences, effects or outcomes of a certain treatment strategy can be expressed in several ways such as for example: number of life years gained, number of symptom-free days, points of BP reduction, or quality adjusted life years (QALY's). The latter combines both the quantity and quality of life. HRQoL outcomes, expressed as utility values, simply known as utilities, are used to calculate QALY's. Utilities usually range between 0 (death) and 1 (perfect health), although values below 0 exist (health states that are perceived worse than death). A variety of tools can be used to assess utilities e.g. EQ-5D; Quality of well-being scale (QWB); Health Utility Index (HUI); 6 dimensional health state classification (SF-6D); 15 dimensional instrument (15D); Assessment of Quality of Life (AQol). Despite the discussion concerning different cost-utility outcomes, depending on the utility measure used, the general advice on cost-utility analyses is to make use of EQ-5D utility values whenever possible (National Institute for Health and Care Excellence, 2013).

QALY's are calculated by multiplying this utility value with the number of life years a patient spends in a certain utility state.

The incremental cost-effectiveness ratio (ICER) is calculated as the ratio of the difference in cost between both treatments and the difference in QALY's between the two treatments (Drummond et al, 2005).

$$\text{ICER}=\frac{(C_{\text{New}} - C_{\text{Current}})}{(E_{\text{New}} - E_{\text{Current}})}$$

ICER= incremental cost-effectiveness ratio
C= costs
E= effect/outcome often expressed as QALY's

A higher ratio indicates a worse result for the new treatment modality. Whether or not a treatment will be considered cost-effective, depends on the willingness of the society to pay for each additional year in perfect health (1 QALY). Depending on the geographical area different willingness-to-pay thresholds are being used. According to the WHO, the wealth of a country should determine the cost-effectiveness threshold. Hence, a ICER below the Gross Domestic Product (GDP) per person in a given country can be considered as cost-effective. In western European countries a cost-effectiveness threshold of 30,000€/QALY is frequently used (Annemans, 2008). Often a range is being applied. The UK uses an ICER threshold range of £20,000 to £30,000 per QALY. Some countries use an ICER threshold based on passed resource allocation decision, such as Australia: AU$69,9000/QALY; New Zealand: NZ$20,000/QALY; Canada: acceptance range: <CAN$80,000/QALY; rejection range: CAN$31,000 to CAN$137,000 per QALY. In the USA a threshold of $50,000/QALY and in the Netherlands a threshold of 80,000€/QALY is proposed (Cleemput et al, 2008)

To goal of todays health care is to produce health. In the past, decisions about reimbursement of/ investment in therapeutic or preventive actions were not always organized in a consistent matter. They were often taken because 'this is what we did last time', or based on 'an educated guess' (Drummond et al, 2005). With the increasing health care expenses in many countries, health care payers need to find adequate ways for decision making. Within most countries attempts are being made to standardize the decision making regarding investment and reimbursement, by defining a set of criteria. In addition to effectiveness, safety, social need and feasibility, more interest is going to cost-effectiveness and budget impact (Cleemput et al, 2008; World Health Organisation, 2013b). However decision making remains a complex process, not only based on rational assessment of problems, alternatives or best solutions but also on political considerations (Cleemput et al, 2008).

Chapter 3.
Validity and reliability of the instruments

Based on:

De Smedt D, Clays E, Doyle F, Kotseva K, Prugger C, Pająk A, Jennings C, Wood D, De Bacquer D, On behalf of the EUROASPIRE Study Group

Validity and reliability of three commonly used quality of life measures in a large European population of coronary heart disease patients.

International Journal of Cardiology (2013); 167(5): 2294-9

Abstract

Objective: To investigate the validity and reliability of the EuroQol-5D (EQ-5D), the 12-item Short-Form Health Survey (SF-12), and the Hospital Anxiety and Depression Scale (HADS) in a stable coronary population.

Study design: Cross-sectional study EUROASPIRE III.

Setting: Health-related quality of life (HRQoL)/psychological distress data were available on 8745 patients hospitalized for coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), acute myocardial infarction (AMI), or myocardial ischemia. They were interviewed and examined at least 6 months after their hospital admission. Reliability and validity of the 3 instruments were tested. Internal consistency, and discriminative, convergent, criterion and construct validity were assessed.

Results: Cronbach's alpha indicated good internal consistency for all measures (0.73 to 0.87). Discriminative validity analyses confirmed significant HRQoL/psychological distress differences between known groups: age, gender, educational level. In addition, all hypothesized correlations between HRQoL/psychological distress constructs (convergent validity) and items (criterion validity) were confirmed with significant correlations. Confirmatory factor analyses indicated good construct validity for HADS and SF-12. On country-specific level, results were roughly similar.

Conclusion: The EQ-5D as well as the SF-12 and the HADS are reliable and valid instruments for use in a stable coronary population, both on aggregate European level and on country-specific level. However, our results must be generalized with caution, because EUROASPIRE III patients might not be representative for all patients with stable coronary heart disease.

1. Introduction

Due to improved cardiovascular prevention and management, coronary heart disease (CHD) death rates have decreased in Western, Northern, and Southern European countries during the last decades (Allender et al, 2008; Leal et al, 2006). Despite this reduction, CHD remains the most common cause of disease burden throughout Europe. Conventional medicine focuses mainly on clinical measures and functional outcomes; however, the use of health-related quality of life (HRQoL) instruments has become increasingly important to assess the patient's emotional, social and physical well-being (Celano et al, 2011; Cepeda-Valery et al, 2011). Patients suffering from CHD are likely to have an impaired HRQoL, due to pain, anxiety, functional and social limitations (Dyer et al, 2010; Mols et al, 2009; Thombs et al, 2006; Xie et al, 2008). Although still under debate, several studies have observed a relationship between HRQoL, depression, anxiety and worse long-term health outcomes (Burstrom et al, 2001; DeSalvo et al, 2006; Meijer et al, 2011; Nicholson et al, 2006; Roest et al, 2010). Many HRQoL measures are available, and most of them have been comprehensively tested in the general population with regard to their reliability and validity. In addition, different studies have assessed the psychometric properties of HRQoL instruments in various disease-specific samples, including CHD patients; however in general, cross-European data were limited (Bjelland et al, 2002; Coons et al, 2000; Cosco et al, 2012; Haywood et al, 2005).

Within the EUROASPIRE III program (EUROpean Action on Secondary and Primary Prevention through Intervention to Reduce Events), a multicentre European survey developed to assess how clinical guidelines on cardiovascular disease prevention are implemented throughout Europe, HRQoL/psychological distress assessment was performed on the basis of 3 questionnaires: the EuroQol-5D (EQ-5D) (The EuroQol Group, 1990; Rabin et al, 2011), the 12-item Short-Form Health Survey (SF-12) (Ware et al, 1996), and the Hospital Anxiety and Depression Scale (HADS) (Zigmond et al, 1983).

EQ-5D is a widely used simple, generic instrument to measure health in a standardized way. The measure is applicable to a wide range of conditions and treatments and contains a self-classifier and a visual analogue scale. Based on the self-classifier, a single index value can be calculated, representing the overall health status (Rabin et al, 2011; Rabin et al, 2001). Another commonly used health status questionnaire is the SF-12, a downsized version of the SF-36 and therefore useful for large studies. The measure allows to calculate a Physical Component Summary (PCS-12) score and a Mental Component Summary (MCS-12) score (Ware et al, 1996). In addition to these general health measures, specific instruments are available for assessing anxiety, depression or depressive symptoms; feelings that are highly common in coronary patients (Roest et al, 2010; Thombs et al, 2006). In order to adapt treatment accordingly, screening for depressive feelings and anxiety is important. The HADS instrument permits to calculate both anxiety (HADS-A) and depression (HADS-D) scores.

The present study investigates the psychometric properties of the EQ-5D, SF-12 and HADS instruments in a large multi-country European cross-sectional sample of coronary patients, the EUROASPIRE III survey.

2. Methods

Study population and data collection

Analyses were based on data gathered during the EUROASPIRE III survey. The details of the study have been reported elsewhere (Kotseva et al, 2009b). In brief, EUROASPIRE III, performed in 2006–2007 among patients with established CHD, is a cross-sectional study aimed at determining whether the European recommendations of cardiovascular disease prevention are being followed in daily practice. Patients, aged 80 years or less, hospitalized for coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), acute myocardial infarction (AMI) or myocardial ischemia were retrospectively identified from diagnostic registers, hospital discharge lists or other sources at 76 different hospital centres in 22 European countries: Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, Romania, Russia, Slovenia, Spain, The Netherlands, Turkey, and the United Kingdom (UK). Data collection was conducted by trained research staff using standardized methods and instruments. Of the 13,935 patients identified, 8966 were interviewed and examined at least 6 months and not later than 3 years after their index hospital admission. In addition to the collection of disease related clinical measures, patients were asked to fill in 3 self-administered questionnaires related to HRQoL and perceived overall health status: EQ-5D, HADS and SF-12. In each country, questionnaires were administered in the official language. EQ-5D contains a self-classifier (EQ-5D$_{index}$) and a visual analogue scale (EQ-VAS). The former is made up of five Likert-scale items covering the following dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. A single summary index, according to the weighting system derived by Dolan (Dolan, 1997) is derived from the answers given on the self-classifier; with 1 representing perfect health, 0 representing death, and <0 representing a health state perceived worse than death (Dolan, 1997; Rabin et al, 2001). The EQ-VAS is a 20-cm vertical scale, ranging between 0 (worst imaginable health state) and 100 (best imaginable health state) on which the respondent is asked to indicate how good or bad his or her health is today. The SF-12 consists of 12 questions, with 3 to 5 response levels, and is intended to asses both physical and mental functioning, represented by a Physical Component Summary (PCS-12) score and a Mental Component Summary (MCS-12) score respectively. The PCS-12 and MCS-12 scores were calculated based on a US general population scoring algorithm (Ware et al, 2002). Results are represented by a value ranging between 0 and 100, with 0 representing the lowest level of health and 100 the highest level of health. The SF-12 was not administered in Hungary. In Germany, the SF-36 was used instead of the SF-12; however, an overall physical and mental component score could be calculated using the SF-12 items embedded in the SF-36. The HADS, intended for use in a hospital setting, contains 14 items, each with a four-point response scale. Seven items are related to anxiety and the other 7 items to depression. The instrument gives information about possible or probable anxiety or depressive feelings, but it is not appropriate in screening for clinical depression. Item scores can be added to obtain the summary scores on anxiety (HADS-A) and depression (HADS-D) separately. The total score on each subscale ranges between 0 and 21. A score <8 can be considered as being in the normal range, higher scores can indicate a possible or probable disorder (Stafford et al, 2007; Zigmond et al, 1983).

Psychometric analyses

Psychometrics aims to evaluate the reliability and validity of measures by assessing the characteristics of scales (Hays et al, 1993). Stratification by country, gender, age and educational level was performed. Four age groups were considered: <50 years, 50–59 years, 60–69 years and >70 years. And 3 educational levels were used: primary education, defined as primary school or less; secondary education, defined as secondary school completed, high school completed or intermediate between secondary level completed; and high education, defined as a university/college degree or equivalent. Patient records for which no summary score could be calculated were excluded from the analyses.

Reliability

Internal consistency of the EQ-5D self-classifier, PCS-12, MCS-12, HADS-A and HADS-D was examined using the Cronbach's coefficient alpha (Hays et al, 1993). A threshold of 0.7 was considered acceptable, a value >0.8 indicated good internal consistency, and a value >0.9 indicated excellent internal consistency (Nunnally & Bernstein, 1994).

Validity

Confirmatory factor analysis (CFA) for the SF-12 and HADS measures was conducted in order to test whether the original scale construct was confirmed in this sample. No CFA was performed for EQ-5D since this measure does not include different theoretical constructs. The Weighted Least Squares Mean and Variance adjusted (WLSMV) estimation method was used for ordinal data. Multiple goodness of fit tests were used, including the Root Mean Square Error of Approximation (RMSEA), the Comparative Fit Index (CFI) and the Tucker–Lewis Index (TLI). Since it is well known that the overall χ^2 fit index is largely influenced by sample size, tending to over-reject models with large sample size, this index was not used in drawing conclusions (Hu et al, 1999). For CFI and TLI, a threshold value >0.9 was considered as a good fit (Bentler et al, 1980). Whereas for the RMSEA, a value <0.06 was considered as a good fit, a value <0.08 was considered as an acceptable fit and a value >0.1 led to rejection of the model (Brown et al, 1992; Hu et al, 1999). Factor loadings represent the correlation between observed variables and extracted components. Standardized factor loadings >0.5 were perceived as good, loadings >0.4 indicated an acceptable correlation and those <0.4 were perceived as not good. Discriminative validity was examined with the known-group method by assessing the relationship of the HRQoL constructs with age, gender and education. Non-parametric tests (Kruskall–Wallis) were used due to the skewed nature of the data. We hypothesized that HRQoL would decrease with age and lower education, and would be lower in female patients. Convergent validity was evaluated with the Spearman's correlations for theoretically correlated constructs. Constructs capturing similar functional or emotional characteristics were expected to highly correlate with one another. Correlations <0.3 were considered as negligible, a value between 0.3 and 0.5 as moderate and >0.5 as strong (Cohen, 1988). It was hypothesized that MCS-12 would correlate with HADS-A and HADS-D and that the two HADS scales would correlate with each other. Furthermore, it was expected that the EQ-5D$_{index}$ would correlate with PCS-12 and MCS-12. In addition, the EQ-VAS was considered as the criterion for overall health; hence, a correlation between EQ-VAS and PCS-12, MCS-12 and EQ-5D$_{index}$ was expected. Likewise, the first question of the SF-12 instrument (SF-12/1), asking about the general state of an individual's health, was also considered as a criterion of overall health. The SF-12/1 was hypothesized to correlate with EQ-5D$_{index}$ and the EQ-VAS. Similarly the EQ-5D anxiety/depression item and question 6c of the SF-12 item (SF-12/6c) “Have you felt downhearted and depressed?” were considered as an overall criterion for anxiety and depression. Therefore, these items were expected to correlate with both HADS-A and HADS-D. All the analyses were performed using IBM SPSS 19, except the CFA, which was conducted using M-plus version 6.11.

3. Results

General characteristics

The patient characteristics are presented in Table 1. In total, data on 8745 patients from 22 European countries are included in the psychometric analyses, ranging from 120 Greek patients to 550 patients from Germany. The majority of the patients were male (74.6%) and their mean age was 63.2 ±9.5 years. Regarding educational level, about a quarter (25.3%) of the patients had a primary education. More than half (56.7%) of the patients had a secondary education and 18.0% had a higher education. Mean values of the different HRQoL scales and subscales are shown in Table 2. Intraclass correlation coefficients (ICCs) were calculated for all HRQoL measures, in order to assess the proportion of variance due to the grouping structure on country-level. ICCs indicated a significant proportion of variance that could be assigned to the countries. Variation in HADS-A and HADS-D scores amounted to 5.70% and 5.37% respectively. For EQ-5D and EQ-VAS, ICC values of 4.92% and 8.26% were observed respectively. Country grouping explained 8.44% and 5.67% in the variation of PCS-12 and MCS-12 scores respectively.

Reliability

The overall Cronbach's alpha for the EQ-5D self-classifier equals 0.73, indicating an acceptable internal consistency of the measure (see Table 3). The variation between countries ranged between 0.58 and 0.82. Ten countries had a value <0.70, indicating less acceptable internal reliability. The SF-12 subscales had higher Cronbach's alpha values with an overall value of 0.87 and 0.84 for PCS-12 and MCS-12 respectively. Country-specific values for PCS-12 ranged between 0.81 and 0.90, indicating good to excellent internal consistency. For MCS-12, Cronbach's alpha values ranged between 0.74 and 0.89, indicating acceptable to good internal consistency. In addition, for both HADS scales satisfying values were found overall, with a value of 0.82 and 0.74 for HADS-A and HADS-D respectively. For HADS-A Cronbach's alpha ranged between 0.73 and 0.86; for HADS-D, values fluctuated between 0.52 and 0.82, with only 2 countries (Germany and Latvia) having a value <0.7.

Table 1: Patient characteristics of the EUROASPIRE population

	Number of patients	Gender (%male)	Age (mean ±SD)	Education level		
				Primary (%)	Secondary (%)	High (%)
All Countries	8745	74.6	63.2±9.5	25.3	56.7	18.0
Belgium	281	85.4	62.4±8.8	16.3	61.6	22.1
Bulgaria	538	69.5	64.8±10.4	3.6	63.1	33.3
Cyprus	434	87.3	61.1±9.3	41.3	42.1	16.6
Czech Rep.	475	79.2	62.9±8.6	3.0	80.3	16.7
Germany	550	79.3	63.7±9.1	6.4	80.0	13.6
Spain	505	74.7	62.0±9.7	70.3	23.9	5.8
Finland	237	66.7	66.2±9.9	17.7	76.4	5.9
France	303	78.3	62.2±10.4	44.9	45.9	9.2
UK	322	73.6	63.0±9.8	8.5	66.3	25.2
Greece	120	88.3	62.4±9.6	33.3	37.5	29.2
Croatia	450	77.1	61.2±9.3	22.9	60.7	16.4
Hungary	457	58.0	63.8±8.5	23.9	49.6	26.5
Ireland	385	76.9	62.5±9.6	59.7	34.8	5.5
Italy	377	79.3	65.2±9.1	39.9	53.2	6.9
Lithuania	509	77.8	63.0±8.8	8.5	60.8	30.7
Latvia	519	65.7	66.2±8.4	17.6	60.2	22.2
Netherlands	223	81.6	64.8±8.9	26.3	67.2	6.5
Poland	502	69.9	62.6±8.8	32.3	50.0	17.7
Romania	521	72.6	61.7±9.8	10.4	74.4	15.2
Russia	409	64.3	64.9±10.1	7.8	54.1	38.1
Slovenia	293	73.0	64.8±9.7	32.1	57.7	10.2
Turkey	335	80.6	59.8±10.1	56.7	31.4	11.9

Validity

CFA of the HADS 2-factor model suggested a good construct validity with the observed data fitting well with the theoretical model. The Bentler's CFI, TLI and RMSEA (0.96, 0.96 and 0.06 respectively), indicated a good fit and factor loadings >0.55 were found, representing a good correlation between observed variables and extracted components. The CFA of the SF-12 allowed for covariations between the error of the items that belong to one overall question (2a and 2b; 3a and 3b; 4a and 4b; 6a, 6b and 6c). Again, Bentler's CFI, TLI and RMSEA indices indicated acceptable to good fit (0.98, 0.98 and 0.09 respectively) and good correlation between observed variables and extracted components was seen with factor loadings ranging between 0.55 and 0.83. Known-group discriminative validity analyses confirmed that all HRQoL measures distinguished well between patient groups with a different age, gender or educational level (Table 2). Male patients had significantly lower HADS-A and HADS-D scores, and higher EQ-5D$_{index}$, EQ-VAS, PCS-12 and MSC-12 scores compared to females. Significant differences for all measures were found between all three educational levels, with lower HRQoL values in lower educated patients. Higher anxiety, lower depression, higher EQ-5D$_{index}$, EQ-VAS, PCS-12 and MCS-12 were found in younger patients compared to the older ones. On country-specific level, the above reported results were roughly similar. A correlation matrix for the different constructs or items can be found in Table 4. All theoretically hypothesized correlations were confirmed. There was a strong correlation among the mental health scores HADS-A, HADS-D and MCS-12. Also, the overall health score EQ-5D$_{index}$ correlated strongly with PCS-12 and moderately with MCS-12.

Table 2: Mean values of the different constructs

	HADS-A	HADS-D	EQ-5D$_{index}$	EQ-VAS	PCS-12	MCS-12
All Countries	5.93	5.08	0.76	65.66	42.14	49.15
Belgium	5.91	4.99	0.82	72.53	45.13	49.25
Bulgaria	6.74	5.92	0.77	63.26	42.16	50.31
Cyprus	4.68	3.68	0.81	69.97	47.49	52.85
Czech Rep.	4.59	4.89	0.76	65.40	41.41	49.58
Germany	5.29	5.64	0.76	67.66	42.47	51.37
Spain	7.09	5.29	0.73	66.75	39.39	46.42
Finland	4.87	4.32	0.78	74.03	38.01	53.62
France	6.59	5.61	0.71	66.66	41.63	44.42
UK	6.16	4.47	0.71	73.34	41.93	49.36
Greece	6.44	4.90	0.80	68.85	46.51	50.82
Croatia	6.64	5.22	0.73	63.74	41.21	48.21
Hungary	6.66	5.45	0.70	66.30	-	-
Ireland	5.64	3.26	0.81	73.60	45.37	51.91
Italy	5.10	4.23	0.86	75.08	47.08	51.43
Lithuania	6.03	4.85	0.74	58.93	38.70	48.69
Latvia	4.30	4.65	0.84	55.52	43.93	50.42
Netherlands	4.28	3.40	0.85	75.74	47.08	52.77
Poland	7.21	5.65	0.73	60.75	38.78	46.37
Romania	5.78	4.86	0.75	69.32	41.13	49.39
Russia	7.18	6.67	0.65	59.51	36.74	45.85
Slovenia	7.01	6.49	0.66	62.93	40.21	46.91
Turkey	5.96	6.01	0.77	69.13	45.73	44.08
Significance	*	*	*	*	*	*
Gender						
Men	5.48	4.75	0.78	67.85	43.20	49.93
Women	7.24	6.01	0.69	62.22	38.82	46.75
Significance	*	*	*	*	*	*
Age						
<50 year	6.35	4.42	0.81	71.43	45.59	48.84
50-59 years	6.12	4.73	0.77	67.48	43.31	48.94
60-69 years	5.71	5.05	0.76	66.72	42.16	49.57
>70 years	5.89	5.70	0.72	63.03	39.56	48.90
Significance	*	*	*	*	*	*
Education level						
Primary education	6.55	5.61	0.72	64.87	40.95	47.98
Secondary education	5.85	5.04	0.76	66.44	41.95	49.27
High education	5.31	4.40	0.80	68.32	44.28	50.44
Significance	*	*	*	*	*	*

* Kruskall Wallis p-value <0.0001

Criterion validity was confirmed for PCS-12, MCS-12 and EQ-5D$_{index}$ given the correlations with EQ-VAS as criterion for overall health perception. Likewise, EQ-5D$_{index}$ and EQ-VAS showed good correlations with the overall health criterion SF-12/1. Both HADS-A and HADS-D correlated moderate to strong with the individual mental health items EQ-5D anxiety/depression and SF-12/6c.

Table 3: Internal consistency

	Cronbach's alpha				
	EQ-5D$_{index}$	**SF-12 PCS**	**SF-12 MCS**	**HADS-A**	**HADS-D**
All Countries	0.73	0.87	0.84	0.82	0.74
Belgium	0.68	0.88	0.87	0.77	0.80
Bulgaria	0.76	0.90	0.88	0.84	0.78
Cyprus	0.67	0.85	0.84	0.83	0.77
Czech Rep.	0.68	0.85	0.79	0.84	0.78
Germany	0.67	-	-	0.80	0.52
Spain	0.72	0.84	0.87	0.81	0.82
Finland	0.67	0.88	0.82	0.77	0.72
France	0.67	0.86	0.87	0.83	0.77
UK	0.80	0.89	0.87	0.86	0.82
Greece	0.75	0.86	0.89	0.79	0.76
Croatia	0.75	0.87	0.84	0.82	0.77
Hungary	0.71	-	-	0.84	0.80
Ireland	0.67	0.86	0.80	0.81	0.72
Italy	0.76	0.89	0.89	0.77	0.75
Lithuania	0.66	0.87	0.80	0.77	0.70
Latvia	0.58	0.84	0.74	0.73	0.62
Netherlands	0.68	0.87	0.85	0.80	0.77
Poland	0.73	0.84	0.82	0.82	0.72
Romania	0.73	0.81	0.81	0.85	0.76
Russia	0.74	0.88	0.85	0.79	0.70
Slovenia	0.80	0.84	0.89	0.80	0.74
Turkey	0.82	0.87	0.81	0.84	0.81

4. Discussion

Psychometric evaluations of the HADS, EQ-5D and SF-12 measures were performed in this study. Our study has the advantage that it comprises data on 8745 coronary patients, spread over 22 European countries. This is, to our knowledge, the largest study assessing the psychometric aspects of 3 different HRQoL questionnaires in a coronary population. Patients included were stable coronary patients, suffering from an event 6 months to 3 years prior to the interview. Data collection was organized in a standardized way by trained research staff, making the data suitable for comparison across patients and countries. Coding of the data and data analyses were performed in a systematic way.

Table 4: Correlation between domains

	HADS-D	EQ-5D$_{index}$	EQ-5D anx/depr	EQVAS	PCS-12	MCS-12	SF12-1	SF12-6c
HADS-A	0.60(0.36 to 0.73)	-0.51(-0.31 to -0.61)	0.57(0.24 to 0.67)	-0.36(-0.13 to -0.53)	-0.34(-0.16 to -0.47)	-0.59(-0.31 to -0.71)	0.36(0.11 to 0.52)	-0.58(-0.32 to -0.70)
HADS-D		-0.51(-0.22 to -0.63)	0.45(0.24 to 0.56)	-0.45(-0.14 to -0.57)	-0.41(-0.13 to -0.56)	-0.57(-0.22 to -0.69)	0.44(0.26 to 0.56)	-0.51(-0.13 to -0.63)
EQ-5D$_{index}$			-0.62(-0.44 to -0.81)	0.53(0.34 to 0.97)	0.64(0.48 to 0.72)	0.47(0.20 to 0.61)	-0.51(-0.33 to -0.63)	0.50(0.32 to 0.56)
EQ-5D anx/depr				-0.34(-0.25 to -0.42)	-0.26(-0.10 to -0.39)	-0.54(-0.42 to -0.63)	0.31(0.16 to 0.46)	-0.55(-0.47 to -0.66)
EQVAS					0.55(0.35 to 0.67)	0.41(0.23 to 0.57)	-0.60(-0.48 to -0.73)	0.38(0.24 to 0.47)
PCS-12						0.19(-0.14 to 0.44)	-0.68(-0.51 to -0.75)	0.29(0.07 to 0.35)
MCS-12							-0.38(-0.15 to -0.57)	0.76(0.63 to 0.86)
SF12-1								-0.38(-0.24 to -0.47)

EQ-5D anx/depr: EQ-5D anxiety/depression. All correlations are significant ($p<0.05$)

Previous studies often included analyses on only 1 single measure and in 1 specific region or country (Bjelland et al, 2002; Cosco et al, 2012; Ellis et al, 2005; Failde et al, 2010; Schweikert et al, 2006). Overall, favourable results were found, supporting the use of these HRQoL measures in a European coronary population. Internal consistency was confirmed for all the HRQoL measures with good to excellent Cronbach's alpha values for the PCS-12 scale, and moderate to good values for the MCS-12 scale and both HADS scales, across all 22 countries. EQ-5D$_{index}$ Cronbach's alpha values were somewhat lower with about half of the countries having a value slightly below 0.70; this is possibly due to the heterogeneity of the questionnaire. In addition, the Cronbach's alpha is sensitive to the number of items, with a tendency to have a smaller value for scales with a limited number of items (Pallant, 2011). A good construct validity was shown for HADS and SF-12. For both HADS and SF-12, the TLI and CFI showed good fit. The RMSEA showed good fit for HADS and a borderline acceptable fit for SF-12. In addition, high factor loadings were observed, indicating a good correlation between observed variables and extracted components for both measures. Discriminative validity for all the HRQoL measures was confirmed. Higher HRQoL values as well as lower depression and anxiety scores were observed in men compared to women. These results support the findings previously reported in the literature (Berg et al, 2010; Cherepanov et al, 2010; Hinz et al, 2011; Johnson et al, 2000; Norris et al, 2008; Xie et al, 2008). Likewise, in agreement with published papers, our study confirms HRQoL differences between groups with different educational levels, with higher EQ-VAS, PCS-12 and MCS-12 scores among the higher educated ones (Failde et al, 2010). As expected, anxiety and depression scores were higher for the lower educated ones. In addition, it was shown that across all groups, age significantly influenced the perceived HRQoL. In general, younger persons had a higher anxiety score but a lower depression score. This is in line with the results reported by Spinhoven et al. (Spinhoven et al, 1997). Likewise, Hinz et al. reported similar results, with lower anxiety scores for older patients (Hinz et al, 2011). In contrast, as confirmed in the literature, older patients had lower EQ-5D$_{index}$, EQ-VAS, PCS-12 and MCS-12 scores (Berg et al, 2010; Johnson et al, 2000). Convergent validity was supported by the correlations found between the different constructs for which an association was theoretically expected. Moderate to strong correlations were observed between the SF-12 constructs and the EQ-5D$_{index}$ and EQ-VAS scores. Strengths were similar to the ones reported by Johnson and Pickard (Johnson et al, 2000). Likewise, a strong correlation was seen among both HADS scales and MCS-12. The strong correlation between SF-12/1 and both the EQ-5D$_{index}$ and EQ-VAS confirmed good criterion validity for EQ-5D$_{index}$ and EQ-VAS. A similar correlation was seen in 2 previously published papers (Ellis et al, 2005; Schweikert et al, 2006). Furthermore, the EQ-VAS correlates well with the EQ-5D$_{index}$ and PCS-12 and correlates moderately with MCS-12. Correlations reported by Ellis et al., between EQ-VAS and the physical and mental components of SF-8 (a derivate from SF-36) were slightly higher (0.77 and 0.55 respectively) (Ellis et al, 2005). The EQ-5D$_{index}$ anxiety component and the SF12-6c as criterion for anxiety and depression, correlated well with both HADS scales. The main limitation of the EUROASPIRE study is its cross-sectional design, making it impossible to compare HRQoL outcomes over a given period of time and to test responsiveness and test–retest reliability. In addition, patients are not a representative sample of all patients with CHD in each country, since they were identified from selected geographical areas and cardiac centres (Kotseva et al, 2009b). While the EQ-5D gives an overall view on a person's general health, the SF-12 clearly distinguishes between mental and physical health. Both measures can be used at any given time, whereas HADS is intended for use in the hospital setting, useful in screening for anxiety and depressive feelings in patients. In order to have an in-depth insight in a patient's HRQoL, it is advised to use a combination of general (e.g. EQ-5D, SF-12), domain-specific (e.g. HADS) and disease-specific (e.g. McNew, Seattle Angina Questionnaire) HRQoL measures, and not to restrict to the use of a single instrument. The integrated HeartQol, a coronary heart disease specific, health-related HRQoL questionnaire, might be a good alternative (Oldridge et al, 2005). In conclusion, the results observed in our study confirm the validity and reliability of the EQ-5D, the SF-12 and the HADS for use in a stable coronary population, both on aggregate European level and on country-specific level. However, our results must be generalized with caution, because EUROASPIRE III patients might not be representative for all patients with stable coronary heart disease.

Chapter 4.
The general population versus coronary patients: EQ-5D outcomes

Based on:

De Smedt D, Clays E, Annemans L, Pardaens S, Kotseva K, De Bacquer D, On behalf of the EUROASPIRE Study Group

Health-Related Quality of life in a European sample of coronary heart disease patients: a comparison with the general population.

European Journal of Cardiovascular Nursing. In press

Abstract

Background: The aim of our study was to compare EuroQoL-5D (EQ-5D) outcomes in Coronary Heart Disease (CHD) patients with those from the general population. We aimed to identify those dimensions mostly impaired.

Methods: EQ-5D results - both the dimensions and the EuroQol Visual Analogue Scale (EQ-VAS) - from a European sample (11 countries) of coronary patients were compared with published age- and gender-specific normative data.

Results: EQ-5D outcomes differed across countries and gender. Overall, the age-adjusted EQ-VAS scores were significantly lower in the coronary patients compared with the general populations, both in males (MD=-5.24[-7.59;-2.88]) and in females (MD=-8.32[-11.69;-4.95]). Coronary patients had a significantly higher risk to report moderate or severe problems related to anxiety/depression (OR male=1.84[1.14;2.95]; OR female=3.20[2.32;4.40]). Furthermore, female coronary patients reported significantly higher problems on the mobility (OR=2.00[1.38;2.90]), usual activity (OR= 2.54[1.81;3.57]) and pain/discomfort dimension (OR=1.73[1.23;2.43]) whereas in males, a borderline significant OR was found on the mobility (OR=1.43[0.97;2.11]) and usual activity dimension (OR=1.44[0.94;2.20]). The difference between the general population and the CHD patients, attenuated as age increased.

Conclusions: CHD has a negative influence on patient's self-reported health status, both the EQ-VAS as well as the EQ-5D dimensions (with the exception of self-care in both genders and pain/discomfort in males) were impaired. The relative impairment was the greatest in female patients and the differences in the proportion of reported problems diminished with increasing age. The EQ-5D instrument is appropriate in capturing problems related to anxiety/depression, pain/discomfort, mobility and usual activities. Within clinical practice, particular attention should be given to females and younger CHD patients.

1. Introduction

Despite the emergence of several medical innovations during the past decades, coronary heart disease (CHD) remains a major health problem, responsible for one out of every five lives lost (Nichols et al, 2012). Furthermore, CHD is also associated with a large morbidity burden with health care expenses amounting to just under 20 billion euro in the European Union in 2009 (Nichols et al, 2012). Conventional medicine is mainly focused on clinical measures and functional outcomes, however, morbidity and mortality rates do not reflect all aspects of health. Over the years patients' self-perceived emotional, social and physical well-being has gained attention, especially in long-term chronic conditions, when full recovery is quite unlikely. Many patients consider the quality of the additional life years gained equally important as the length of life (Thompson et al, 2003). Furthermore, according to some studies self-perceived health is a significant predictor of mortality (Burstrom et al, 2001; Mols et al, 2009). Due to pain, physical and social restrictions, anxiety or depression, cardiovascular patients are particularly vulnerable to have an impaired self-perceived health status, often resulting in a reduced Health-Related Quality of Life (HRQoL) (Mols et al, 2009; Schweikert et al, 2009; Thompson et al, 2003; Xie et al, 2008). A number of measures are being used to assess the importance of disease symptoms and their effect on everyday life as perceived by the patient (Mayou et al, 1993; Swenson et al, 2000). In addition to more generic measures such as Euroqol-5D (EQ-5D) and the 36-Item Short Form Health Survey (SF-36), disease specific measures exist.

Coronary patients often report an impaired health status, however interpretation of the results is difficult, if not impossible in the absence of reference values from the general population. Some studies have investigated the effect of CHD on patients' self-perceived health status compared to normative values (Bradshaw et al, 2006; Brown et al, 1999; Djarv et al, 2012; Lalonde et al, 2001), with one single study making use of the EQ-5D instrument (Schweikert et al, 2009). This study by Schweikert et al., was based on 2950 German patients who had suffered from a myocardial infarction. At follow up (median time since event=7.4 years), the main impairments were seen in the pain/discomfort, usual activities and particularly anxiety/depression dimension. The purpose of our study was to investigate whether their findings could be appraised in a large European sample of coronary patients. EQ-5D information was gathered between 6 months and 3 years after their event (median time since event=1.24 years), allowing us to assess the impact more rapidly after an event.

2. Methods

EQ-5D measure

In order to assess patients' health status, the EQ-5D 3-level instrument was used. This is a cognitively undemanding, easy to complete standardized instrument to measure self-perceived health status. It is intended for self-completion and can be applied to various health conditions and treatments. The instrument comprises two parts: the EQ-5D descriptive system and the EQ-5D visual analogue scale (EQ-VAS). The former has 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 response categories, i.e. 3 levels of severity: no problems, some problems or severe problems; from which a single index value, can be calculated. The EQ-VAS is a 20 cm vertical, visual analogue scale used to record the respondent's self-rated health. The respondent is asked to indicate how good or bad his/her own health status is today. Zero is labelled as the worst imaginable health state and 100 as the best imaginable health state (Rabin et al, 2011; Rabin et al, 2001).

Coronary population-EUROASPIRE III

The EUROASPIRE III survey is a cross-sectional study (2006-07) to determine whether the European recommendations on cardiovascular disease prevention were being followed in everyday clinical practice (Kotseva et al, 2009b). Twenty-two European countries took part in this study, patients aged between 18 and 80 years, and hospitalized for coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), acute myocardial infarction (AMI) or myocardial ischemia were identified retrospectively from diagnostic registers, hospital discharge lists or other sources. At least 6 months and not later than 3 years after their hospital admission, patients were interviewed and examined in a standardized way by trained research staff. To capture information from the index hospital admission, patients' medical records were reviewed. Personal and demographic details as well as personal cardiovascular history, including stroke and transient ischaemic attack were extracted from the medical records. Furthermore, information on other medical history, including hypertension, hyperlipidaemia and diabetes were obtained. Recorded measurements of blood pressure, diabetes, lipids and smoking status and medication (generic name and total daily dose) were gathered if available. At interview, structured questionnaires were used to collect personal and demographic details; personal cardiovascular history, including stroke, transient ischaemic attack and peripheral artery disease; other medical history, including hypertension, hyperlipidaemia and diabetes; family history of CHD for patients with premature disease (men <55 years and women <65 years); reported lifestyle and other risk factor management in relation to smoking, diet (including weight reduction), exercise, blood pressure, lipids and glucose; medication (generic name and total daily dose); and level of education, school attendance and employment status. Furthermore patients were asked to complete validated self-administered questionnaires, among which the EQ-5D in order to assess their health status.

Although the main objective of the EUROASPIRE III study was to describe the lifestyle, risk factor and therapeutic management in patients with coronary heart disease, the collected information allowed investigating the self-perceived health status in coronary patients. More detailed information on the EUROASPIRE III survey can be found elsewhere (Kotseva et al, 2009b).

Normative values-literature

Age-, gender- and country-specific normative HRQoL values were gathered from the literature. An attempt was made to extract the normative data as much as possible from a single report in order to avoid between-study-heterogeneity due to the clinical and methodological variations. Countries for which normative EQ-5D information was not available were excluded from the analyses. EQ-5D information for the general population was available in only half of the 22 EUROASPIRE III countries: Belgium, Finland, Germany, Greece, Hungary, Italy, the Netherlands, Poland, Slovenia, Spain and the United Kingdom. Data on the general population were extracted from a report published by the EuroQol Group (The EuroQol Group's International Task Force on Self-Reported Health, 2004). The publication provides population norms, which can be used as reference data. These age- and gender- specific reference data can be compared to the EQ-5D profiles of patients with specific conditions. Italian and Polish normative data are not included in the EuroQoL report, hence data were extracted from 2 published papers (Golicki et al, 2010; Savoia et al, 2006). More information on how the data was collected can be found in table 1.

Table 1: Details of collected reference data

Belgium	Postal survey on a random sample of people from the Flemish speaking population of Belgium (July, August 2001)
Finland	Postal survey on a random sample of persons chosen from the Finnish computerized population registry (November 1992)
Germany	Postal survey and telephone interviews on a random sample households selected from the German telephone list (June 1994; April 1997; October to March 1998)
Greece	Face to face interviews on a sample individuals selected from the general population (March, April 1998)
Hungary	Interview of a random sample of people from the electoral registry (October to December 2000)
Italy	Postal survey on a random sample from the Registry of the North and South Health Authorities of the city of Bologna (2002)
The Netherlands	Postal survey on a random selection of households based on postal area codes on the right bank of the River Maas in Rotterdam (district with over 20% of immigrants were excluded) (January 1991)
Poland	Face‑to‑face interviews with the visitors of inpatients at 8 Polish medical centers: in Warsaw, Skierniewice, and Puławy forming a representative sample of the Polish adult population (first half 2008)
Slovenia	Postal survey on a randomized sample of people selected from the general population (April, May 2000)
Spain	Face to face interviews on a random sample individuals selected from the general population of a primary health care district on the outskirts of Barcelona, covering 4 different socioeconomic areas (October 1996 to November 1997)
United Kingdom	Face to face interviews on a random sample of individuals selected from the general population from England, Scotland and Wales (August, November 1993).

Statistical analyses

Due to the small sample sizes of coronary patients in younger age groups, only 4 age categories were included in the analyses: 40-49; 50-59; 60-69; 70-79 years. These gender specific age categories were matched with those from the general population. Country-specific normative EQ-5D$_{index}$ values could not be calculated since we had no access to the raw data. Hence analyses are limited to the EQ-VAS and the EQ-5D dimensions. The latter was recoded into 2 categories: no problems reported and problems reported (both some problems or severe problems). Because the age structure in the general population differs from that of the EUROASPIRE III population, direct age standardization was performed (direct age standardization, 1984). For the EQ-VAS, mean differences (MD) between both groups were calculated. For all five EQ-5D dimensions the higher odds for reporting problems in CHD patients compared to the general population, presented as odds ratios (OR), were computed. Results were then summarized with a meta-analytic method using Review Manager 5.1 in order to pool the country-specific data into one overall result. A considerable heterogeneity was observed across countries (I^2 between 70% and 94%). Because the heterogeneity could not be readily explained, random-effect models were used. The default Mantel-Haenszel odd ratio for dichotomous outcomes and the inverse variance mean difference for continuous outcomes were applied. Additional analyses investigating the effect of age were performed in a similar way.

3. Results

Eleven European countries were included in the current analyses. Within the general population, 46.8% of the 11,765 persons with EQ-5D information were male. No information on disease history or education was provided. Furthermore, of the 3775 coronary patients included in the analyses, 74.1% were male. Table 2 shows the main characteristics of both the EUROASPIRE III population as well as the general population data used in our analyses. The main results are presented in table 3, providing a gender-specific comparison of EQ-5D outcomes between CHD patients and the general population. The more extensive graphs representing the proportion of reported problems on each dimension for each country included, are presented in appendix 1. A large variation in reported problems was found across countries and gender, both in the general as well as in the coronary population. Within coronary patients, the lowest proportion of reported problems was seen on the self-care dimension (8% in males and 11% in females) whereas the highest proportion of problems was seen in the pain/discomfort (49% and 66% in males and females resp.) and the anxiety/depression dimension (37% and 60% in males and females resp.). Furthermore 28% of the male CHD patients and 43% of female CHD patients reported problems on the usual activities dimension, and 32% of the male and 43% of the female patients reported problems on the mobility dimension.

Overall, both male and female coronary patients were more likely to report problems regarding anxiety or depression (OR=1.84[1.14-2.95]; OR=3.20[2.32-4.40] resp.) compared with normative data. In addition, female coronary patients had a significantly higher risk to report problems on the pain/discomfort dimension (OR=2.00[1.38;2.90]), mobility dimension (OR= 2.54[1.81:3.57]) and usual activity dimension (OR=1.73[1.23;2.43]).

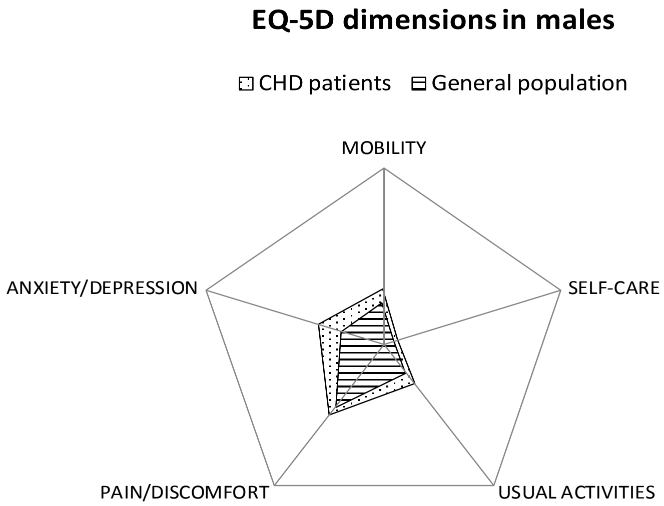
Table 2: Characteristics of the populations included in this analysis.

	EUROASPIRE III		REFERENCE POPULATION	
Characteristics	**N**	**%**	**N**	**%**
Country				
Belgium	278	7.4%	806	6.9%
Finland	221	5.9%	1435	12.2%
Germany	540	14.3%	546	4.6%
Greece	116	3.1%	238	2.0%
Hungary	452	12.0%	3265	27.8%
Italy	362	9.6%	961	8.2%
The Netherlands	500	13.2%	493	4.2%
Poland	282	7.5%	200	1.7%
Slovenia	496	13.1%	386	3.3%
Spain	219	5.8%	1540	13.1%
United Kingdom	309	8.2%	1895	16.1%
Age categories				
40-49 years	295	7.8%	3426	29.1%
50-59 years	969	25.7%	3058	26.0%
60-69 years	1570	41.6%	2944	25.0%
70-79 years	941	24.9%	2337	19.9%
Gender				
Male	2798	74.1%	5503	46.8%
Female	977	25.9%	6262	53.2%
Recruiting event				
CABG	837	22.2%	n.a.	
PCI	1600	42.4%	n.a.	
AMI	605	16.0%	n.a.	
Ischemia	733	19.4%	n.a.	
Education				
Primary education	1084	29.0%	n.a.	
Secondary education	2095	56.1%	n.a.	
High education	556	14.9%	n.a.	
Self-reported diabetes	1005	26.9%	n.a.	
History of stroke	115	3.1%	n.a.	
Recurrent CHD	505	13.4%	n.a.	

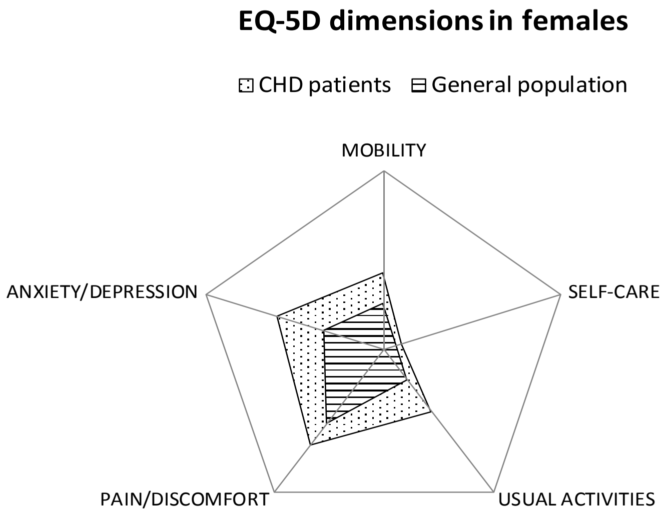
CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; AMI, acute myocardial infarction; Recurrent CHD; Myocardial infarction, acute myocardial ischemia, CABG or PCI since recruiting diagnosis.

Male coronary patients on the contrary, did not have a greater odds to report problems on the pain/discomfort dimension (OR=1.13[0.73;1.73]), but had a borderline significantly higher risk to report problems on the mobility dimension (OR=1.43[0.97;2.11]) and on the usual activity dimension (OR=1.44[0.94;2.20]. Furthermore, coronary patients did not have a higher risk of reporting problems on the self-care dimension (OR=1.27[0.84-1.93]; OR=1.48[0.90-2.46] in males and females resp.). Additional analyses of the reported problems within particular age groups, revealed more problems in older age groups. However, the difference between the general population and the CHD patients, attenuated as age increased (see appendix 2).

Figure 1: Radar chart representing the differences in problems reported in the general population compared to coronary patients



	CHD patients	General population
Mobility	32%	24%
Self-care	8%	7%
Usual activities	28%	20%
Pain/discomfort	49%	44%
Anxiety/depression	37%	24%



	CHD patients	General population
Mobility	43%	26%
Self-care	11%	7%
Usual activities	43%	21%
Pain/discomfort	66%	51%
Anxiety/depression	60%	34%

These graphs present the proportion of problems (some or severe problems) reported by the different groups. The further away from the origin, the more problems reported. CHD: Coronary Heart Disease

Both male as well as female coronary patients had a significantly lower EQ-VAS compared to the general population (MD=-5.24[-7.59;-2.88]; MD=-8.32[-11.69;-4.95] resp.). In an additional analysis we compared the distribution of the EQ-VAS scores between both populations. The 25th percentile of the EQ-VAS scores in the general population (25% of the EQ-VAS observations are smaller than this value) did not correspond with the first quartile of the EUROASPIRE population. The proportion of EUROASPIRE III patients having a value below the general population based 25th percentile, exceeded the expected 25% in most countries. Similar results were seen when looking at the median and the 75th percentile, indicating a shift of the EQ-VAS distribution in EUROASPIRE III patients to the left.

Table 3: Comparison between the coronary patients and the general population

EQ-5D dimension	CHD patients		General population		OR [95% CI] / MD [95% CI]
	Number of patients reporting problems	*Total number of patients*	*Number of patients reporting problems*	*Total number of patients*	
Males					
Mobility	848	2689	1323	5503	1.43[0.97,2.11]
Self-care	221	2689	365	5503	1.27[0.84,1.93]
Usual activities	763	2689	1109	5503	1.44[0.94,2.20]
Pain/discomfort	1327	2689	2405	5503	1.13[0.73,1.73]
Anxiety/depression	989	2689	1306	5503	1.84[1.14,2.95]
EQ-VAS		2652		5474	-5.24[-7.59,-2.88]
Females					
Mobility	404	930	1591	6087	2.00[1.38,2.90]
Self-care	98	930	443	6087	1.48[0.90,2.46]
Usual activities	403	930	1307	6087	2.54[1.81,3.57]
Pain/discomfort	615	930	3122	6087	1.73[1.23,2.43]
Anxiety/depression	557	930	2053	6087	3.20[2.32,4.40]
EQ-VAS		928		6087	-8.32[-11.69,-4.95]

CHD: Coronary Heart Disease, OR: odds ratio, MD: mean difference

4. Discussion

In order to interpret the EQ-5D scores in coronary patients, comparison with general population norms is warranted. Although many studies report on self-reported health status in cardiac patients (Dyer et al, 2010), only few reported on the comparison with reference values. To our knowledge only one study thoroughly compared the EQ-5D results of coronary patients with those from the general population (Schweikert et al, 2009). The study included 2,950 German coronary patients who had suffered from their first MI, 9 months to 22 year ago (median time=7.4 years). Within their study, 79.3% of the respondents were male and their mean age amounted to 68 years. The aim of our study was to investigate whether these results could be confirmed in a similar sample of European coronary patients, suffering from a coronary event, between 6 months and 3 years ago (median time=1.24 years). Dividing the time since the recruiting diagnosis in 2 categories (<1 years and ≥1 year) revealed no significant difference in either EQ-5D dimension, hence the impact of the data collection period seemed limited. Furthermore, due to this shorter follow-up period the results were less likely to be biased by other unmeasured conditions. In accordance with the German study, most problems were reported on the anxiety/depression and pain/discomfort dimension. It should be noted however that this tendency of most frequently reported problem areas is also seen across the general population (The EuroQol Group's International Task Force on Self-Reported Health, 2004). Compared to the German data, the proportion of reported problems on each of the five EQ-5D dimensions was higher in the EUROASPIRE sample, with the exception of the self-care dimension were similar percentages were seen. Surprisingly, the EQ-VAS results reported by Schweikert et al. were slightly worse compared with our findings.

Overall, our results confirm the previously published differences in self-reported health status between coronary patients and the general population. Similar to Schweikert et al, significant differences in reported problems in the pain/discomfort (in females), usual activities and anxiety/depression dimension were found. Likewise, both investigations revealed a significant difference in EQ-VAS scores, whereas no significant effect could be observed in the self-care dimension. In contrast to the German study, a higher proportion of mobility problems was reported in the EUROASPIRE III patients, compared to the general population. Although Schweikert and colleagues speculate that their result might in part be explained by effects of measures of secondary prevention such as higher physical activity, as well as possible selection or information bias, we hypothesize that the discrepancy with our results, is most probably caused by the duration of the follow-up time. Mobility problems are likely to decrease over time, due to partial or full recovery.

In line with the literature, our analyses revealed worse EQ-5D results in females compared to males (Brink et al, 2005; Duenas et al, 2012; Emery et al, 2004; Norris et al, 2010; Phillips-Bute et al, 2003). Despite the general consensus regarding worse self-perceived health outcomes in females, both in the general population as well as in coronary patients, research on the cause of this finding is still on-going. Some argue that women might perceive symptoms in a different way (Norris et al, 2010; Phillips-Bute et al, 2003; van Wijk et al, 1997). Although the latest results indicate that male and female coronary patients experience the same symptoms, some studies found differences in the proportions of symptoms, with women reporting more angina, pain, nausea, fatigue, syncope, weakness, depression and loss of appetite (DeVon et al, 2002; DeVon et al, 2003; Kimble et al, 2003). Physiologic differences might be one of the reasons why women experience worse outcomes. Females for example, have smaller coronary arteries, which might increase ischemia (Lichtman et al, 2008). Furthermore, the higher depression rates in women are strongly associated with poorer recovery rates possibly leading to impaired results (Lichtman et al, 2008). In addition, a lower sense of coherence (SOC) seems to be associated with worse self-perceived health outcomes (Bergman et al, 2012; Pragodpol et al, 2012). This concept assesses whether an individual experiences the world as comprehensible, meaningful and manageable. Among both genders, similar sources including the quality of the relationship with partner, social support, quality of work, and childhood living conditions, are predictors of SOC (Volanen et al, 2004). Both in the general population, as well as in coronary patients, women often have a worse SOC compared to men (Bergman et al, 2012; Eriksson et al, 2006). In accordance, Emery et al. identified perceived social support (meeting and talking regularly with friends and family) as an important predictor of self-perceived health outcome in cardiac women (Emery et al, 2004).

Our results together with those of Schweikert and colleagues confirm the relationship between CHD and anxiety and depression, previously reported by others (Lane et al, 2002; Schweikert et al, 2009; Thombs et al, 2006). Depression and anxiety are common in coronary patients. Approximately 1 out of 5 hospitalized AMI patients suffer from major depression; at 1 year follow up, depression persisted in about half of these patients (Thombs et al, 2006). According to previous EUROASPIRE analyses, based on the Hospital Anxiety and Depression Scale (HADS), within our population the prevalence of depression varied from 8.2% to 35.7% in males and from 10.3% to 62.5% in females; the prevalence of anxiety varied from 12.0% to 41.8% in males and from 21.5% to 63.7% in females (Pajak et al, 2013). These findings suggest that the EQ-5D instrument is an appropriate tool for capturing problems related to anxiety and depression.

Likewise, pain or discomfort are also commonly reported by CHD patients. According to a study by Brown et al (1999) only 43.7% of AMI survivors reported that they were free from chest pain symptoms (Brown et al, 1999). A study by Vetrovec et al (2004) - including patients diagnosed with chronic angina, of whom 56% had received revascularization procedures in the prior year - revealed that 90% of patients had at least one episode of angina in the prior 6 months and more than one in three patients had multiple episodes per week (Vetrovec et al, 2004). Angina is inevitably associated with an impairment in self-perceived health status proportional to the number of angina attacks per week (Pepine et al, 1994). Within CHD patients, EQ-5D adequately captures problems related to pain and discomfort.

Self-care showed to be a less severe problem in CHD patients. This is not surprising, since problems with self-care are more likely to occur during the acute phase of an event, e.g. shortly after a CABG. During this initial recovery period, patients can have more difficulties to wash or dress themselves.

In line with Schweikert et al, the differences in self-reported health status outcomes between coronary patients and the general population, diminished with increasing age, which is probably caused by the increasing comorbidity associated with ageing in the normal population.

It is worthwhile mentioning some strengths and weaknesses regarding this study. Although this study is the first to report on a European cross-country comparison, based on the raw data set of a large population of coronary patients, some limitations should be mentioned. A great variation in odd ratio's and mean differences was seen across country-specific outcomes which can be partially explained by the variation in EQ-5D results across coronary patients from different geographical regions. As previously reported by our research group, the mean CHD-related EQ-5D outcomes vary across EUROASPIRE III countries (De Smedt et al, 2013b). Furthermore, limited information is available on the validity of the reference data. Although the use of these reference data is being proposed by the EuroQol group, these data have not always been collected in the same standardized way, since they were extracted from individual substudies, each with their own specific data collection methods. Hence, some differences in sampling and data collection methods could have occurred in the EuroQol report, however according to the authors there is no reason to believe that these limitations had a significant impact on the results since the EQ-5D is a rather simple and straightforward measure (The EuroQol Group's International Task Force on Self-Reported Health, 2004). In addition, the large time frame, ranging from 1993 until 2008, during which normative data was collected could have had an impact on our findings. Furthermore, information on the general population was only available for half of the EUROASPIRE III countries. Although an attempt was made to avoid heterogeneity between the collected data, by extracting country-specific information from one report as much as possible, considerable heterogeneity remained across the different countries, hence random effect model analyses were performed. Furthermore, we were not able to account for socioeconomic status, income and education since this information was not available for the general population data.

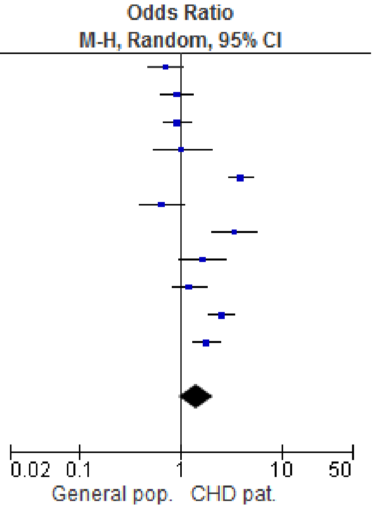
In conclusion, our results have shown that the self-perceived health status in coronary patients is significantly worse compared to the general population, with the exception of self-care in both genders and pain/discomfort in males. We observed higher proportions of reported problems compared to the study performed by Schweikert et al., in which EQ-5D information was collected much later after the event, suggesting that impairments improve somewhat over time. The EQ-5D instrument appears to be an appropriate tool for capturing problems with regard to anxiety/depression, pain/discomfort, mobility and usual activities. Furthermore the tool differentiates significantly between women and men, with female CHD patients reporting a greater relative impairment. Within clinical practice particular attention should be given to the self-perceived health status of females and younger CHD patients. In addition to the individual burden on a patient’s live, self-perceived health status is also associated with future mortality and morbidity as well as with increased health care expenses, hence actions to tackle these impairments are needed (Burstrom et al, 2001; DeSalvo et al, 2006). Lifestyle changes are shown to be associated with better self-perceived outcomes, hence patients should be encouraged and supervised to change their behaviour in order to adopt a healthier lifestyle (De Smedt et al, 2013a). Future research should be aimed at investigating further interventions or treatment schemes possibly associated with improvements in self-perceived health status. Furthermore, since country-specific normative EQ-5D information is rather scarce, there is a need for a coordinated cross-country collection of EQ-5D information, with well-defined inclusion criteria and additional collection of covariates. This will allow easy comparison between the general population and several patient groups (not limited to CHD patients).

APPENDIX 1: Comparison between the coronary patients and the general population (age standardization)

MOBILITY
MALES

	CHD pat.		General pop.			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
BELGIUM	43	233	94	386	9.2%	0.70 [0.47, 1.05]
FINLAND	51	148	263	723	9.3%	0.92 [0.63, 1.33]
GERMANY	104	416	98	369	9.6%	0.92 [0.67, 1.27]
GREECE	19	101	24	130	7.8%	1.02 [0.53, 1.99]
HUNGARY	142	260	331	1403	9.7%	3.90 [2.96, 5.12]
ITALY	23	261	60	461	8.7%	0.65 [0.39, 1.07]
NETHERLANDS	55	167	26	205	8.6%	3.38 [2.00, 5.70]
POLAND	107	314	22	92	8.6%	1.64 [0.97, 2.80]
SLOVENIA	108	207	88	185	9.2%	1.20 [0.81, 1.79]
SPAIN	116	363	111	715	9.6%	2.56 [1.89, 3.45]
UK	80	217	206	834	9.6%	1.78 [1.30, 2.45]
Total (95% CI)		**2687**		**5503**	**100.0%**	**1.43 [0.97, 2.11]**
Total events	848		1323			

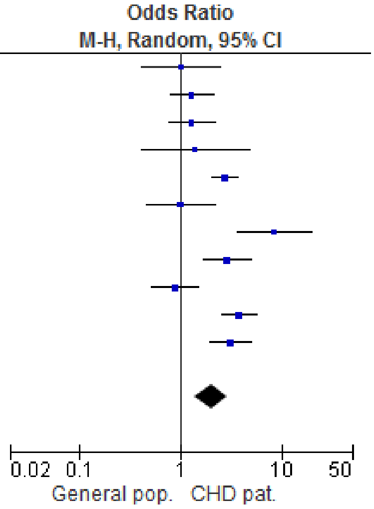
Heterogeneity: $Tau^2 = 0.38$; $Chi^2 = 110.39$, df = 10 ($P < 0.00001$); $I^2 = 91\%$
Test for overall effect: Z = 1.81 (P = 0.07)



FEMALES

	CHD pat.		General pop.			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
BELGIUM	6	39	64	420	7.1%	1.01 [0.41, 2.51]
FINLAND	37	73	240	537	10.2%	1.27 [0.78, 2.07]
GERMANY	36	107	50	177	10.0%	1.29 [0.77, 2.16]
GREECE	4	14	24	108	5.2%	1.40 [0.40, 4.86]
HUNGARY	105	189	584	1862	11.4%	2.74 [2.02, 3.70]
ITALY	8	62	65	500	7.9%	0.99 [0.45, 2.18]
NETHERLANDS	13	39	16	288	7.6%	8.50 [3.69, 19.59]
POLAND	62	130	26	108	9.6%	2.88 [1.64, 5.03]
SLOVENIA	32	75	92	201	9.8%	0.88 [0.52, 1.51]
SPAIN	62	123	176	825	10.9%	3.75 [2.54, 5.54]
UK	39	79	254	1061	10.4%	3.10 [1.95, 4.92]
Total (95% CI)		**930**		**6087**	**100.0%**	**2.00 [1.38, 2.90]**
Total events	404		1591			

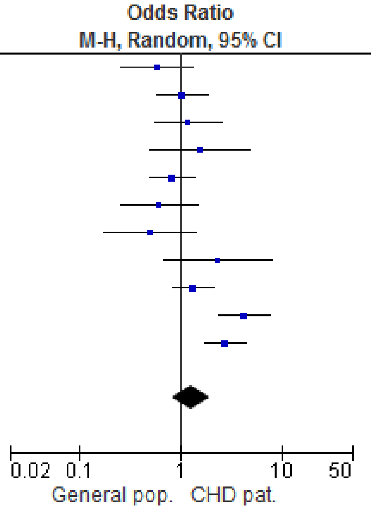
Heterogeneity: $Tau^2 = 0.29$; $Chi^2 = 49.75$, df = 10 ($P < 0.00001$); $I^2 = 80\%$
Test for overall effect: Z = 3.67 (P = 0.0002)



SELF-CARE
MALES

Study or Subgroup	CHD pat. Events	CHD pat. Total	General pop. Events	General pop. Total	Weight	Odds Ratio M-H, Random, 95% CI
BELGIUM	8	235	22	386	8.6%	0.58 [0.26, 1.33]
FINLAND	14	148	66	723	10.2%	1.04 [0.57, 1.91]
GERMANY	16	416	12	369	9.1%	1.19 [0.56, 2.55]
GREECE	7	101	6	130	6.7%	1.54 [0.50, 4.73]
HUNGARY	18	260	116	1403	10.9%	0.83 [0.49, 1.38]
ITALY	7	261	20	461	8.3%	0.61 [0.25, 1.46]
NETHERLANDS	5	167	12	205	7.1%	0.50 [0.17, 1.44]
POLAND	23	314	3	92	6.1%	2.34 [0.69, 7.99]
SLOVENIA	54	207	39	185	11.2%	1.32 [0.83, 2.11]
SPAIN	36	363	18	715	10.4%	4.26 [2.38, 7.62]
UK	33	217	51	834	11.2%	2.75 [1.73, 4.39]
Total (95% CI)		**2689**		**5503**	**100.0%**	**1.27 [0.84, 1.93]**
Total events	221		365			

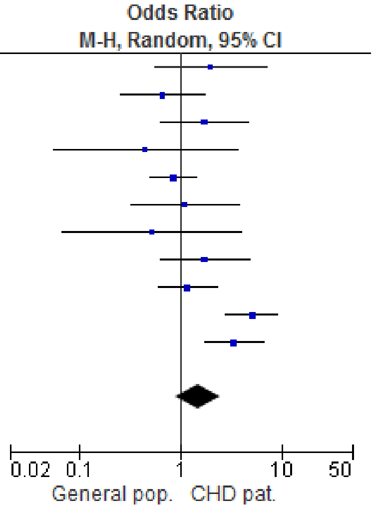
Heterogeneity: Tau² = 0.35; Chi² = 39.65, df = 10 (P < 0.0001); I² = 75%
Test for overall effect: Z = 1.12 (P = 0.26)



FEMALES

Study or Subgroup	CHD pat. Events	CHD pat. Total	General pop. Events	General pop. Total	Weight	Odds Ratio M-H, Random, 95% CI
BELGIUM	3	39	17	420	7.6%	1.98 [0.55, 7.06]
FINLAND	5	73	54	537	9.6%	0.66 [0.25, 1.70]
GERMANY	8	107	8	177	9.2%	1.71 [0.62, 4.69]
GREECE	1	14	16	108	4.1%	0.44 [0.05, 3.62]
HUNGARY	16	189	183	1862	12.6%	0.85 [0.50, 1.45]
ITALY	3	62	22	500	7.8%	1.10 [0.32, 3.80]
NETHERLANDS	1	39	14	288	4.3%	0.52 [0.07, 4.03]
POLAND	12	130	6	108	9.2%	1.73 [0.63, 4.77]
SLOVENIA	16	75	38	201	11.7%	1.16 [0.60, 2.24]
SPAIN	21	123	32	825	12.2%	5.10 [2.83, 9.18]
UK	12	79	53	1061	11.6%	3.41 [1.74, 6.68]
Total (95% CI)		**930**		**6087**	**100.0%**	**1.48 [0.90, 2.46]**
Total events	98		443			

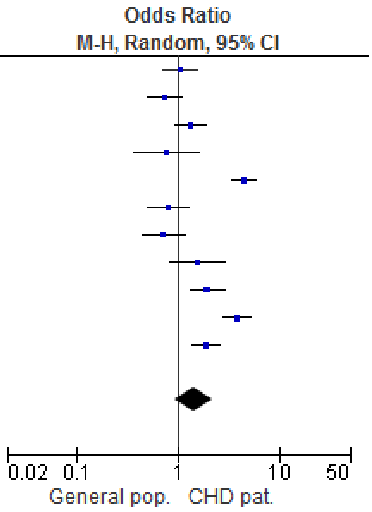
Heterogeneity: Tau² = 0.45; Chi² = 33.44, df = 10 (P = 0.0002); I² = 70%
Test for overall effect: Z = 1.54 (P = 0.12)



USUAL ACTIVITIES
MALES

Study or Subgroup	CHD pat. Events	CHD pat. Total	General pop. Events	General pop. Total	Weight	Odds Ratio M-H, Random, 95% CI
BELGIUM	49	235	78	386	9.3%	1.04 [0.70, 1.55]
FINLAND	36	148	221	723	9.3%	0.73 [0.49, 1.10]
GERMANY	92	416	65	369	9.5%	1.33 [0.93, 1.89]
GREECE	13	101	21	130	7.7%	0.77 [0.36, 1.62]
HUNGARY	132	260	263	1403	9.7%	4.47 [3.39, 5.90]
ITALY	29	261	63	461	9.0%	0.79 [0.49, 1.26]
NETHERLANDS	32	167	51	205	8.9%	0.72 [0.43, 1.18]
POLAND	69	314	14	92	8.3%	1.57 [0.84, 2.94]
SLOVENIA	118	207	75	185	9.3%	1.94 [1.30, 2.91]
SPAIN	120	363	81	715	9.6%	3.87 [2.81, 5.31]
UK	73	217	177	834	9.5%	1.88 [1.36, 2.61]
Total (95% CI)		**2689**		**5503**	**100.0%**	**1.44 [0.94, 2.20]**
Total events	763		1109			

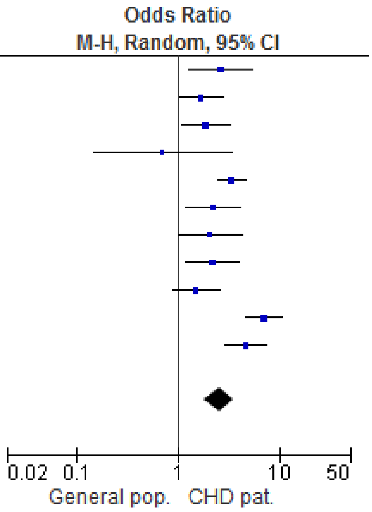
Heterogeneity: $Tau^2 = 0.46$; $Chi^2 = 122.99$, df = 10 ($P < 0.00001$); $I^2 = 92\%$
Test for overall effect: Z = 1.68 (P = 0.09)



FEMALES

Study or Subgroup	CHD pat. Events	CHD pat. Total	General pop. Events	General pop. Total	Weight	Odds Ratio M-H, Random, 95% CI
BELGIUM	13	39	67	420	8.2%	2.63 [1.29, 5.39]
FINLAND	34	73	183	537	10.1%	1.69 [1.03, 2.76]
GERMANY	32	107	33	177	9.5%	1.86 [1.06, 3.26]
GREECE	2	14	21	108	3.4%	0.69 [0.14, 3.32]
HUNGARY	95	189	426	1862	11.7%	3.41 [2.51, 4.62]
ITALY	16	62	68	500	9.0%	2.21 [1.18, 4.12]
NETHERLANDS	12	39	51	288	7.9%	2.07 [0.98, 4.35]
POLAND	43	130	20	108	9.1%	2.17 [1.18, 3.99]
SLOVENIA	42	75	92	201	9.8%	1.51 [0.88, 2.57]
SPAIN	72	123	138	825	10.9%	7.03 [4.70, 10.51]
UK	42	79	208	1061	10.4%	4.66 [2.92, 7.43]
Total (95% CI)		**930**		**6087**	**100.0%**	**2.54 [1.81, 3.57]**
Total events	403		1307			

Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 42.18$, df = 10 ($P < 0.00001$); $I^2 = 76\%$
Test for overall effect: Z = 5.40 ($P < 0.00001$)



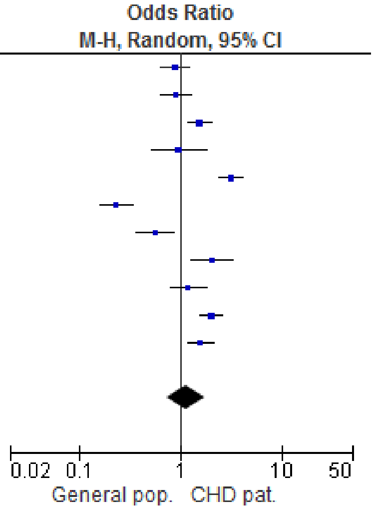
PAIN/DISCOMFORT

MALES

Study or Subgroup	CHD pat. Events	CHD pat. Total	General pop. Events	General pop. Total	Weight	Odds Ratio M-H, Random, 95% CI
BELGIUM	106	235	187	386	9.3%	0.87 [0.63, 1.21]
FINLAND	79	148	404	723	9.2%	0.90 [0.63, 1.29]
GERMANY	239	416	173	369	9.4%	1.53 [1.15, 2.03]
GREECE	21	101	28	130	8.1%	0.96 [0.51, 1.81]
HUNGARY	182	260	597	1403	9.4%	3.15 [2.37, 4.19]
ITALY	48	261	229	461	9.2%	0.23 [0.16, 0.33]
NETHERLANDS	55	167	96	205	8.9%	0.56 [0.37, 0.85]
POLAND	196	314	41	92	8.8%	2.07 [1.29, 3.31]
SLOVENIA	125	207	104	185	9.0%	1.19 [0.79, 1.78]
SPAIN	165	363	210	715	9.5%	2.00 [1.54, 2.60]
UK	111	217	336	834	9.4%	1.55 [1.15, 2.10]
Total (95% CI)		**2689**		**5503**	**100.0%**	**1.13 [0.73, 1.73]**
Total events	1327		2405			

Heterogeneity: $Tau^2 = 0.49$; $Chi^2 = 168.29$, $df = 10$ ($P < 0.00001$); $I^2 = 94\%$

Test for overall effect: $Z = 0.55$ ($P = 0.58$)

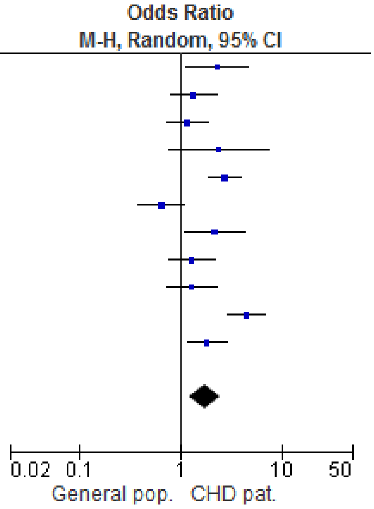


FEMALES

Study or Subgroup	CHD pat. Events	CHD pat. Total	General pop. Events	General pop. Total	Weight	Odds Ratio M-H, Random, 95% CI
BELGIUM	28	39	221	420	7.9%	2.29 [1.11, 4.72]
FINLAND	51	73	342	537	9.5%	1.32 [0.78, 2.25]
GERMANY	61	107	94	177	9.9%	1.17 [0.72, 1.90]
GREECE	7	14	32	108	5.3%	2.38 [0.77, 7.32]
HUNGARY	149	189	1077	1862	10.8%	2.72 [1.89, 3.90]
ITALY	24	62	248	500	9.4%	0.64 [0.37, 1.10]
NETHERLANDS	23	39	115	288	8.3%	2.16 [1.10, 4.27]
POLAND	79	130	59	108	9.6%	1.29 [0.77, 2.16]
SLOVENIA	53	75	131	201	9.1%	1.29 [0.72, 2.29]
SPAIN	94	123	345	825	10.2%	4.51 [2.91, 6.99]
UK	46	79	458	1061	10.0%	1.84 [1.15, 2.92]
Total (95% CI)		**930**		**6087**	**100.0%**	**1.73 [1.23, 2.43]**
Total events	615		3122			

Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 44.10$, $df = 10$ ($P < 0.00001$); $I^2 = 77\%$

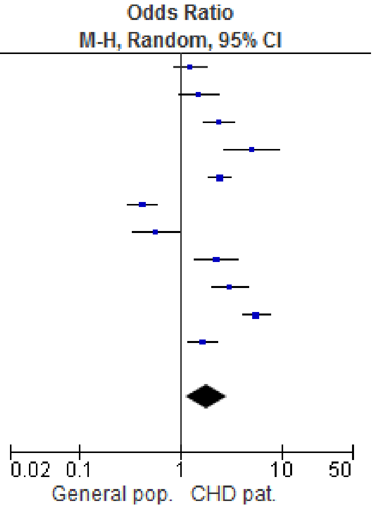
Test for overall effect: $Z = 3.13$ ($P = 0.002$)



ANXIETY/DEPRESSION
MALES

Study or Subgroup	CHD pat. Events	CHD pat. Total	General pop. Events	General pop. Total	Weight	Odds Ratio M-H, Random, 95% CI
BELGIUM	61	235	85	386	9.2%	1.24 [0.85, 1.81]
FINLAND	27	148	93	723	8.9%	1.51 [0.94, 2.42]
GERMANY	123	416	55	369	9.3%	2.40 [1.68, 3.42]
GREECE	45	101	18	130	8.3%	5.00 [2.65, 9.42]
HUNGARY	143	260	469	1403	9.5%	2.43 [1.86, 3.18]
ITALY	59	261	190	461	9.3%	0.42 [0.30, 0.59]
NETHERLANDS	25	167	49	205	8.7%	0.56 [0.33, 0.95]
POLAND	164	314	30	92	8.9%	2.26 [1.39, 3.68]
SLOVENIA	129	207	65	185	9.1%	3.05 [2.02, 4.61]
SPAIN	147	363	77	715	9.4%	5.64 [4.11, 7.73]
UK	66	217	175	834	9.3%	1.65 [1.18, 2.30]
Total (95% CI)		**2689**		**5503**	**100.0%**	**1.84 [1.14, 2.95]**
Total events	989		1306			

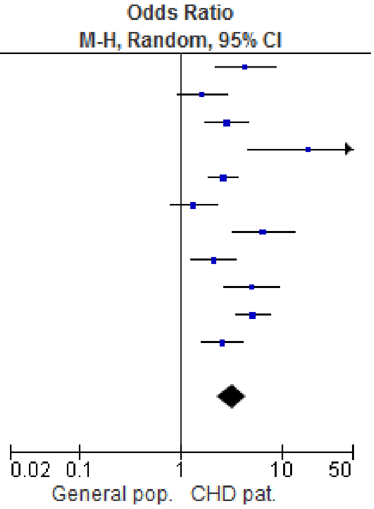
Heterogeneity: $Tau^2 = 0.60$; $Chi^2 = 166.46$, df = 10 ($P < 0.00001$); $I^2 = 94\%$
Test for overall effect: $Z = 2.52$ ($P = 0.01$)



FEMALES

Study or Subgroup	CHD pat. Events	CHD pat. Total	General pop. Events	General pop. Total	Weight	Odds Ratio M-H, Random, 95% CI
BELGIUM	22	39	96	420	8.3%	4.37 [2.23, 8.56]
FINLAND	18	73	90	537	9.2%	1.63 [0.91, 2.90]
GERMANY	60	107	55	177	10.0%	2.83 [1.72, 4.66]
GREECE	11	14	18	108	3.8%	18.33 [4.64, 72.38]
HUNGARY	136	189	918	1862	11.5%	2.64 [1.90, 3.67]
ITALY	30	62	206	500	9.7%	1.34 [0.79, 2.27]
NETHERLANDS	20	39	40	288	7.9%	6.53 [3.20, 13.29]
POLAND	84	130	50	108	9.7%	2.12 [1.26, 3.57]
SLOVENIA	60	75	89	201	8.7%	5.03 [2.68, 9.46]
SPAIN	77	123	201	825	10.9%	5.20 [3.49, 7.74]
UK	39	79	290	1061	10.3%	2.59 [1.63, 4.11]
Total (95% CI)		**930**		**6087**	**100.0%**	**3.20 [2.32, 4.40]**
Total events	557		2053			

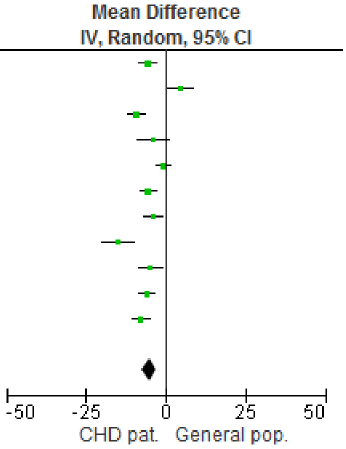
Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 38.36$, df = 10 ($P < 0.0001$); $I^2 = 74\%$
Test for overall effect: $Z = 7.14$ ($P < 0.00001$)



EQ-VAS
MALES

Study or Subgroup	CHD pat. Mean	SD	Total	General pop. Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
BELGIUM	72.5	17.6	233	78.2	14.2	386	9.7%	-5.70 [-8.37, -3.03]
FINLAND	76.6	23.6	147	71.9	18.7	723	8.3%	4.70 [0.65, 8.75]
GERMANY	68.3	18.4	425	77.6	18.4	369	9.8%	-9.30 [-11.87, -6.73]
GREECE	72.1	19.5	97	75.9	18.6	130	7.4%	-3.80 [-8.83, 1.23]
HUNGARY	66.9	17	256	67.8	19.5	1403	10.0%	-0.90 [-3.22, 1.42]
ITALY	77	15.6	287	82.6	18	461	9.9%	-5.60 [-8.04, -3.16]
NETHERLANDS	77.1	13	141	80.9	15.6	205	9.4%	-3.80 [-6.83, -0.77]
POLAND	63.2	20	304	78.3	18	63	7.4%	-15.10 [-20.08, -10.12]
SLOVENIA	66.5	18.9	206	71.3	18.8	185	8.7%	-4.80 [-8.54, -1.06]
SPAIN	68.6	19.3	353	74.6	18	715	9.9%	-6.00 [-8.41, -3.59]
UK	73.4	18.6	203	81.3	16.9	834	9.6%	-7.90 [-10.70, -5.10]
Total (95% CI)			**2652**			**5474**	**100.0%**	**-5.24 [-7.59, -2.88]**

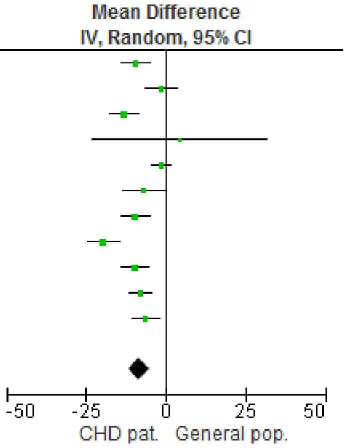
Heterogeneity: Tau² = 13.03; Chi² = 66.52, df = 10 (P < 0.00001); I² = 85%
Test for overall effect: Z = 4.36 (P < 0.0001)



FEMALES

Study or Subgroup	CHD pat. Mean	SD	Total	General pop. Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
BELGIUM	70.5	13.1	35	80	14.7	420	9.9%	-9.50 [-14.06, -4.94]
FINLAND	69.6	20.8	73	71	19	537	9.5%	-1.40 [-6.43, 3.63]
GERMANY	65.6	20.5	110	78.8	17.7	177	9.8%	-13.20 [-17.83, -8.57]
GREECE	76.8	50.1	13	72.6	19.2	108	1.3%	4.20 [-23.27, 31.67]
HUNGARY	62.1	19.1	184	63.5	19.6	1862	11.1%	-1.40 [-4.30, 1.50]
ITALY	65.8	29.6	75	72.6	18	500	8.0%	-6.80 [-13.68, 0.08]
NETHERLANDS	71.1	13.5	38	80.7	16.5	288	9.8%	-9.60 [-14.30, -4.90]
POLAND	59.2	21	131	78.9	18	108	9.6%	-19.70 [-24.65, -14.75]
SLOVENIA	61.5	14.9	75	71.2	19.5	201	10.1%	-9.70 [-14.02, -5.38]
SPAIN	64	18.3	121	71.9	18.7	825	10.7%	-7.90 [-11.40, -4.40]
UK	73.8	18.6	73	80.2	17.5	1061	10.0%	-6.40 [-10.79, -2.01]
Total (95% CI)			**928**			**6087**	**100.0%**	**-8.32 [-11.69, -4.95]**

Heterogeneity: Tau² = 24.49; Chi² = 55.34, df = 10 (P < 0.00001); I² = 82%
Test for overall effect: Z = 4.83 (P < 0.00001)



These tables give an overview of country and gender specific comparisons between the EUROASPIRE III patients and the general population. As can be seen from the tables a large variation exists between countries and between men and women. CHD: Coronary Heart Disease; events are defined as some or severe problems reported.

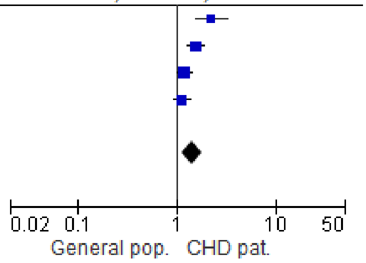
APPENDIX 2: Comparison between the coronary patients and the general population (age groups)

MOBILITY

MALES

	CHD pat.		General pop.			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
45 years	41	192	176	1614	18.0%	2.22 [1.52, 3.24]	
55 years	214	702	320	1457	26.7%	1.56 [1.27, 1.91]	
65 years	376	1112	419	1393	28.3%	1.19 [1.00, 1.41]	
75 years	286	683	408	1039	27.0%	1.11 [0.92, 1.36]	
Total (95% CI)		**2689**		**5503**	**100.0%**	**1.40 [1.11, 1.78]**	
Total events	917		1323				

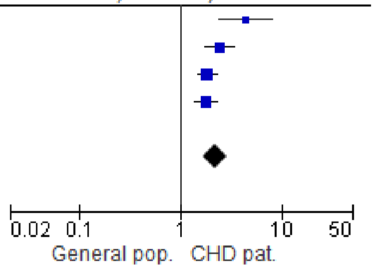
Heterogeneity: Tau² = 0.04; Chi² = 14.15, df = 3 (P = 0.003); I² = 79%
Test for overall effect: Z = 2.79 (P = 0.005)



FEMALES

	CHD pat.		General pop.			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
45 years	18	51	201	1812	14.1%	4.37 [2.42, 7.91]	
55 years	64	159	348	1601	24.8%	2.43 [1.73, 3.40]	
65 years	183	399	490	1551	31.2%	1.83 [1.47, 2.30]	
75 years	188	321	573	1298	29.9%	1.79 [1.40, 2.29]	
Total (95% CI)		**930**		**6262**	**100.0%**	**2.20 [1.67, 2.91]**	
Total events	453		1612				

Heterogeneity: Tau² = 0.05; Chi² = 9.34, df = 3 (P = 0.03); I² = 68%
Test for overall effect: Z = 5.58 (P < 0.00001)

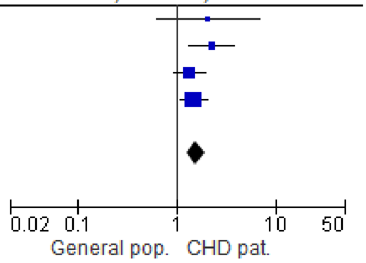


SELF-CARE

MALES

	CHD pat.		General pop.			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
45 years	3	51	54	1812	3.3%	2.03 [0.61, 6.74]	
55 years	18	159	86	1601	16.3%	2.25 [1.32, 3.85]	
65 years	41	399	122	1551	33.8%	1.34 [0.92, 1.95]	
75 years	63	321	184	1298	46.7%	1.48 [1.08, 2.03]	
Total (95% CI)		**930**		**6262**	**100.0%**	**1.55 [1.25, 1.92]**	
Total events	125		446				

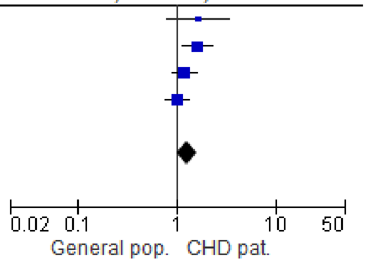
Heterogeneity: Tau² = 0.00; Chi² = 2.72, df = 3 (P = 0.44); I² = 0%
Test for overall effect: Z = 3.96 (P < 0.0001)



FEMALES

	CHD pat.		General pop.			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
45 years	9	192	47	1614	9.0%	1.64 [0.79, 3.40]	
55 years	63	702	84	1457	27.2%	1.61 [1.15, 2.26]	
65 years	92	1112	98	1393	31.4%	1.19 [0.89, 1.60]	
75 years	89	683	136	1039	32.4%	0.99 [0.75, 1.32]	
Total (95% CI)		**2689**		**5503**	**100.0%**	**1.26 [0.99, 1.59]**	
Total events	253		365				

Heterogeneity: Tau² = 0.02; Chi² = 5.18, df = 3 (P = 0.16); I² = 42%
Test for overall effect: Z = 1.88 (P = 0.06)

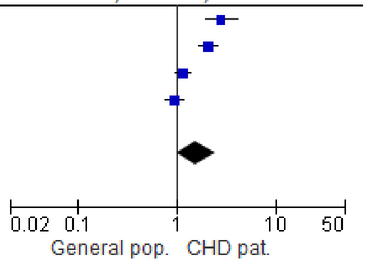


USUAL ACTIVITIES

MALES

Study or Subgroup	CHD pat. Events	CHD pat. Total	General pop. Events	General pop. Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
45 years	48	192	171	1614	22.9%	2.81 [1.96, 4.04]	
55 years	234	702	285	1457	25.6%	2.06 [1.68, 2.52]	
65 years	288	1112	323	1393	25.9%	1.16 [0.96, 1.39]	
75 years	208	683	331	1039	25.6%	0.94 [0.76, 1.15]	
Total (95% CI)		**2689**		**5503**	**100.0%**	**1.56 [1.00, 2.42]**	
Total events	778		1110				

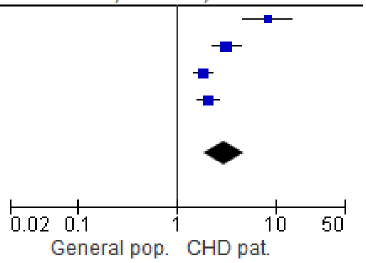
Heterogeneity: Tau² = 0.19; Chi² = 46.38, df = 3 (P < 0.00001); I² = 94%
Test for overall effect: Z = 1.96 (P = 0.05)



FEMALES

Study or Subgroup	CHD pat. Events	CHD pat. Total	General pop. Events	General pop. Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
45 years	26	51	201	1812	20.5%	8.34 [4.72, 14.71]	
55 years	67	159	300	1601	25.3%	3.16 [2.25, 4.43]	
65 years	153	399	391	1551	27.2%	1.85 [1.46, 2.33]	
75 years	165	321	438	1298	27.0%	2.08 [1.62, 2.66]	
Total (95% CI)		**930**		**6262**	**100.0%**	**2.97 [1.85, 4.76]**	
Total events	411		1330				

Heterogeneity: Tau² = 0.20; Chi² = 27.28, df = 3 (P < 0.00001); I² = 89%
Test for overall effect: Z = 4.53 (P < 0.00001)

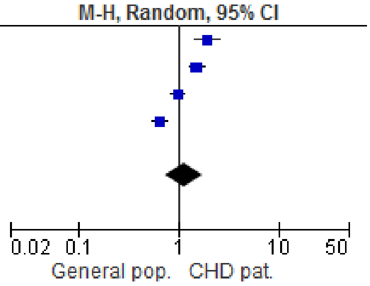


PAIN/DISCOMFORT

MALES

Study or Subgroup	CHD pat. Events	CHD pat. Total	General pop. Events	General pop. Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
45 years	87	192	488	1614	23.5%	1.91 [1.41, 2.59]	
55 years	365	702	612	1457	25.5%	1.50 [1.25, 1.79]	
65 years	542	1112	688	1393	25.7%	0.97 [0.83, 1.14]	
75 years	329	683	617	1039	25.3%	0.64 [0.52, 0.77]	
Total (95% CI)		**2689**		**5503**	**100.0%**	**1.14 [0.74, 1.76]**	
Total events	1323		2405				

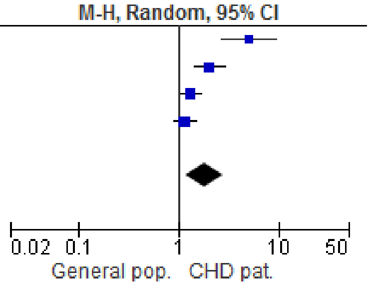
Heterogeneity: Tau² = 0.18; Chi² = 56.05, df = 3 (P < 0.00001); I² = 95%
Test for overall effect: Z = 0.61 (P = 0.54)



FEMALES

Study or Subgroup	CHD pat. Events	CHD pat. Total	General pop. Events	General pop. Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
45 years	38	51	671	1812	18.6%	4.97 [2.63, 9.40]	
55 years	108	159	818	1601	25.6%	2.03 [1.43, 2.87]	
65 years	257	399	899	1551	28.2%	1.31 [1.04, 1.65]	
75 years	208	321	802	1298	27.7%	1.14 [0.88, 1.47]	
Total (95% CI)		**930**		**6262**	**100.0%**	**1.81 [1.16, 2.80]**	
Total events	611		3190				

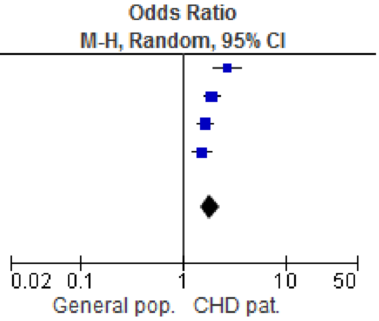
Heterogeneity: Tau² = 0.16; Chi² = 22.17, df = 3 (P < 0.0001); I² = 86%
Test for overall effect: Z = 2.64 (P = 0.008)



ANXIETY/DEPRESSION
MALES

Study or Subgroup	CHD pat. Events	CHD pat. Total	General pop. Events	General pop. Total	Weight	Odds Ratio M-H, Random, 95% CI
45 years	75	192	310	1614	18.9%	2.70 [1.97, 3.70]
55 years	293	702	398	1457	27.2%	1.91 [1.58, 2.30]
65 years	383	1112	336	1393	28.2%	1.65 [1.39, 1.97]
75 years	231	683	264	1039	25.6%	1.50 [1.21, 1.85]
Total (95% CI)		**2689**		**5503**	**100.0%**	**1.84 [1.51, 2.24]**
Total events	982		1308			

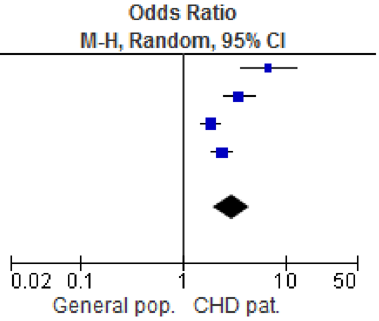
Heterogeneity: Tau² = 0.03; Chi² = 10.40, df = 3 (P = 0.02); I² = 71%
Test for overall effect: Z = 5.99 (P < 0.00001)



FEMALES

Study or Subgroup	CHD pat. Events	CHD pat. Total	General pop. Events	General pop. Total	Weight	Odds Ratio M-H, Random, 95% CI
45 years	37	51	507	1812	18.2%	6.80 [3.65, 12.69]
55 years	104	159	561	1601	25.5%	3.51 [2.49, 4.94]
65 years	204	399	561	1551	28.4%	1.85 [1.48, 2.30]
75 years	181	321	457	1298	27.8%	2.38 [1.86, 3.05]
Total (95% CI)		**930**		**6262**	**100.0%**	**2.96 [1.95, 4.49]**
Total events	526		2086			

Heterogeneity: Tau² = 0.15; Chi² = 20.79, df = 3 (P = 0.0001); I² = 86%
Test for overall effect: Z = 5.11 (P < 0.00001)



Chapter 5.
Association HRQoL and risk profile in coronary patients

Based on:

De Smedt D, Clays E, Annemans L, Doyle F, Kotseva K, Pająk A, Prugger C, Jennings C, Wood D, De Bacquer D, On behalf of the EUROASPIRE Study Group

Health related quality of life in coronary patients and its association with their cardiovascular risk profile: Results from the EUROASPIRE III survey

International Journal of Cardiology (2013); 168(2): 898-903

Abstract

Background: Cardiovascular patients are likely to have an impaired Health-Related Quality of Life (HRQoL) due to functional and psycho-social limitations. The main objective of this study was to assess the distribution of HRQoL scores in coronary heart disease (CHD) patients across 22 European countries and to identify factors associated with the variation between patients.

Methods: Data from the EUROASPIRE III survey (European Action on Secondary and Primary Prevention by Intervention to Reduce Events), on 8734 patients, were used. Patients with a diagnosis of CHD (coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), acute myocardial infarction (AMI) or myocardial ischemia) were interviewed and examined at least 6 months after their acute coronary event. HRQoL of each patient was measured using 2 standardized questionnaires: the EuroQoL-5D (EQ-5D) and the 12-item short-form health survey (SF-12).

Results: HRQoL values differed significantly across countries. Lower HRQoL estimates were found in women, older patients, less educated patients, patients with myocardial infarction or ischemia as recruiting diagnosis, patients with a history of stroke and patients who suffered from a recurring CHD event. In addition, HRQoL was significantly associated with current smoking, central obesity, lack of exercise and inappropriate HbA1c control in patients with diabetes. Furthermore the number of risk factors is inversely associated with HRQoL.

Conclusion: Overall, a large heterogeneity was observed in HRQoL values between countries and patient groups. There seems to be a significant association between HRQoL and patient characteristics with lifestyle risk factors as important determinants of HRQoL.

1. Introduction

Cardiovascular disease (CVD) remains the most common cause of disease burden in Europe, with coronary heart disease (CHD) being the single most important cause of death (Allender et al, 2008). Conventional treatment focuses mainly on functional outcomes, survival and extending life. However, morbidity and mortality rates are incomplete measures of outcome, since they do not reflect all aspects of health. Many patients consider the quality of the additional life years gained equally important as the length of life. Indeed, the goal of today's medicine should be to increase both patients' quantity and quality of life (Oldridge et al, 2005). In response, assessment of health-related quality of life (HRQoL) has been increasingly integrated in daily clinical practice. HRQoL is a subjective measure of overall well-being and reflects how a disease and its symptoms are perceived by a patient. Although there is no universal agreement on what constitutes HRQoL, current assessment focuses on the domains of social functioning, physical functioning and psychological functioning (Swenson et al, 2000). CHD patients are known to have an impaired HRQoL (Xie et al, 2008). Recent studies have shown a significant influence of HRQoL on long-term outcomes. Poor HRQoL has been shown to predict morbidity and mortality in patients with CHD, even when controlling for standard risk factors (Grool et al, 2012; Rumsfeld et al, 1999; Spertus et al, 2002). The aim of our study was to examine the relationship between the cardiovascular profile of coronary patients and their HRQoL. Data were derived from the EUROASPIRE III (European Action on Secondary and Primary Prevention by Intervention to Reduce Events) survey wherein two commonly used instruments were employed to assess patient's HRQoL: the EQ-5D (EuroQol-5D) and the SF-12 (12-item short-form health survey).

2. Methods

Study population and data collection

The details of the EUROASPIRE III study have been reported elsewhere (Kotseva et al, 2009b). In brief, EUROASPIRE III, performed in 2006-07 in patients with established CHD, was a cross-sectional study to determine whether the European recommendations on CVD prevention were being followed in everyday clinical practice. Patients aged between 18 and 80 years, hospitalized for coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), acute myocardial infarction (AMI) or myocardial ischemia, hereafter referred to as the recruiting diagnosis, were retrospectively identified from diagnostic registers, hospital discharge lists or other sources at 76 different hospital centres across 22 European countries: Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, Romania, Russian Federation, Slovenia, Spain, The Netherlands, Turkey, and the United Kingdom (UK). Data collection was conducted by trained research staff using standardized methods and instruments. In total, 8966 patients (participation rate=73%) were interviewed and examined at least 6 months and not later than 3 years after their initial hospital admission (median time=1.24 years). Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (Coats et al, 2011).

Patient characteristics and risk factors assessed

The interview contained questions on personal and demographic details; medical and in particularly cardiovascular history (i.e. having a history of stroke or suffering from a recurrent coronary event between the recruiting diagnosis and the moment of interview); reported lifestyle and risk factor management related to smoking, exercise (regular exercise defined as 20-60 min, 3 to 5 times a week), blood pressure, lipids, glucose and medication. In addition, height, weight and waist circumference were measured in light indoor clothes without shoes, as well as blood pressure, heart rate and breath carbon monoxide. Venous blood was tested for serum total cholesterol, HDL-cholesterol (HDL-C), triglycerides, plasma glucose and HbA1c, the latter two were only measured in patient with self-reported diabetes (Kotseva et al, 2009b). LDL-colesterol (LDL-C) was calculated according to the Friedewald formula. The risk factor targets used were based on the European guidelines on cardiovascular prevention (De Backer et al, 2003). A raised blood pressure was defined as systolic blood pressure (SBP)/diastolic blood pressure (DBP) ≥140/90 mm Hg (≥130/80 mm Hg in patients with diabetes). Raised total cholesterol was defined as total cholesterol ≥4.5 mmol/L. Raised LDL-C was defined as LDL-C ≥2.5 mmol/L and low HDL-C was defined as HDL-C <1/1.2 mmol/L for men/women. Raised fasting glucose was defined as fasting glucose ≥6.1 mmol/L among patients with self-reported diabetes and raised HbA1c as HbA1c ≥6.5% among patients with self-reported diabetes. Low physical activity was defined as less than 20 min moderate physical activity, three times a week. Central obesity was defined as waist circumference >102/88 cm (men/women).

Health-related quality of life assessment

In order to assess patients' HRQoL, they were asked to fill out 2 self-administered questionnaires: EQ-5D and SF-12. In each country, the questionnaires were administered in the official language. Validity of these scales has been reported previously (De Smedt et al, 2013b). The EQ-5D is an easy to complete brief instrument that contains a self-classifier (EQ-5D$_{index}$) covering 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a visual analogue scale (EQ-VAS). In the current analyses only the EQ-VAS was included. The EQ-VAS is a vertical scale, ranging from 0 (worst imaginable) to 100 (best imaginable) on which the respondent is asked to indicate their current health state. The SF-12 consists of 12 Likert scale questions, covering 8 dimensions: general health, physical functioning, role-physical, bodily pain, vitality, social functioning, role-emotional and mental health. Both physical (PCS-12) and mental functioning (MCS-12) components can be assessed. The scores were standardized by a common scoring algorithm, ranging between 0 and 100, with lower scores representing worse and higher scores representing better health (Ware et al, 2002). The SF-12 was not administered in Hungary. In Germany, the SF-36 was used instead of the SF-12 (Wee et al, 2008).

Statistical analyses

All analyses were based on generalized linear mixed models in order to account for the clustering of patients within countries. The association between patient characteristics and HRQoL was initially adjusted for gender, age and educational level. A further adjustment for age, gender, educational level, recruiting diagnosis, diabetes, history of stroke, recurring coronary events, smoking, physical activity and central obesity was applied. To investigate the relation between uncontrolled risk factors and HRQoL, in patients being medically treated, adjustment for gender, age, recruiting diagnosis, educational level, diabetes and history of stroke and recurring events was performed. Likewise the relation between the number of risk factors and HRQoL was investigated. In an additional analysis the number of risk factors was considered as a continuous variable, hence a linear regression analysis was performed. In both analyses adjustment for patient characteristics was applied. Significance levels were set at $p < 0.05$. All statistical analyses were performed using the IBM SPSS statistical software (version 20.0).

3. Results

HRQoL data (full information on at least 1 HRQoL instrument) were available for 8734 patients (Table 1). About three quarters (74.6%) of patients included in our analyses were males (n=6516). The average age of patients was 63.2 years (SD=9.5). About 60% of patients included, had a cardiac revascularization as recruiting diagnosis, 19.5% was diagnosed with AMI. The overall mean PCS-12 and MCS-12 were 42.14 (SD=10.15) and 49.15 (SD=10.22) respectively. For the EQ-VAS a mean value of 66.42 (SD=18.84) was observed (Table 2).

Comparison of the HRQoL scores across countries indicated substantial differences, even after adjustment for age, gender, education, recruiting diagnosis, diabetes, history of stroke and recurring events ($p<0.001$) (Fig. 1). There was a tendency towards a poorer HRQoL in patients residing in Eastern European countries.

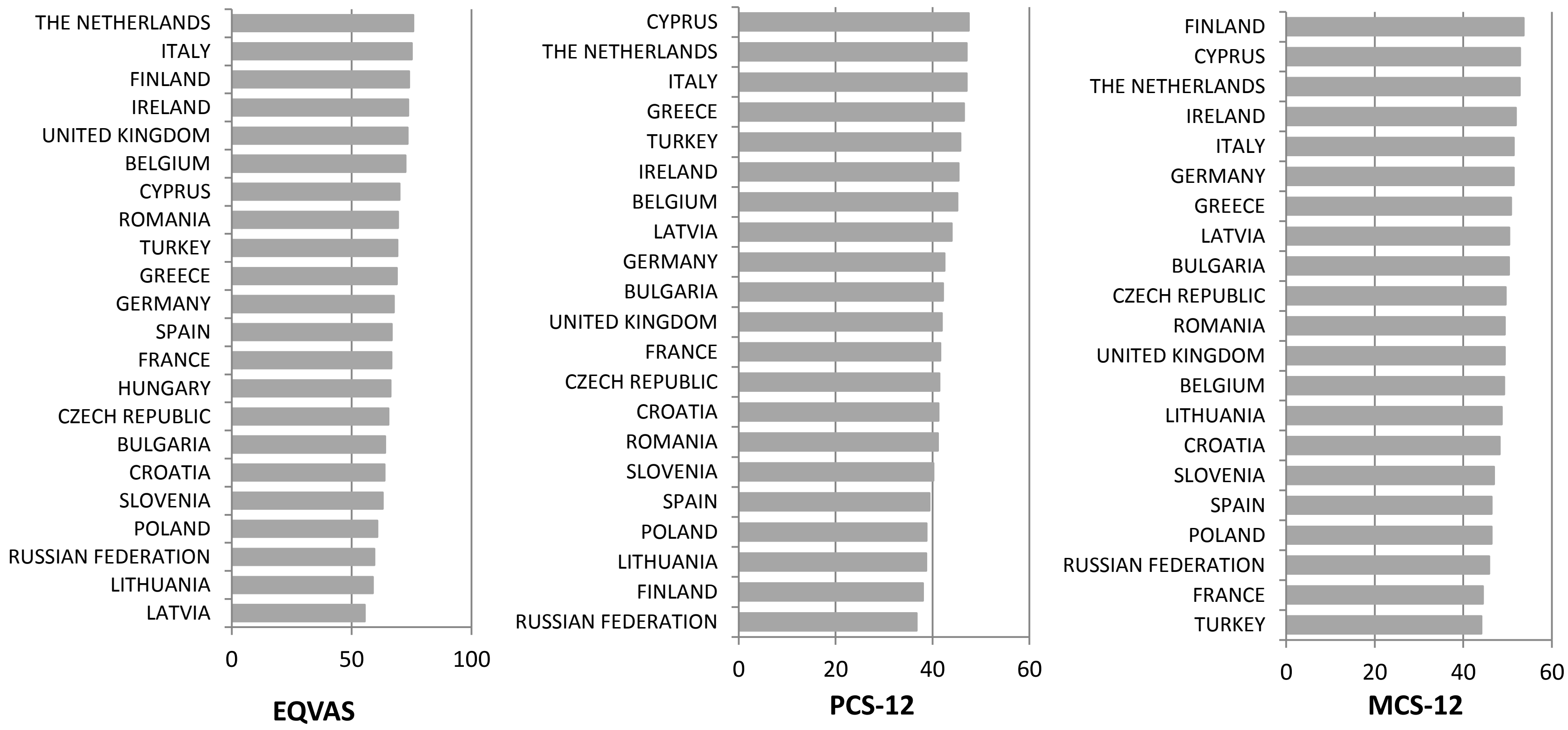
Likewise, gender, age and educational level were significantly associated with HRQoL, with men having a better self-perceived HRQoL compared to women, younger patients scoring higher on physical health and overall well-being, and those with lower education levels having worse HRQoL compared to those with higher levels of education (Tables 2 and 3).

Furthermore, significantly lower HRQoL values were found in patients with self-reported diabetes and higher values in those having undergone cardiac surgery or angioplasty, except for MCS-12, where no significant differences were found between diagnostic categories. In addition, cardiovascular history was also significantly associated with lower HRQoL measures, except for MCS-12, on which recurring events did not have any impact. Finally, better control of lifestyle parameters (central obesity, smoking, physical activity) was significantly associated with HRQoL (except for MCS-12 in central obesity). Based on the regression coefficients from Table 3, these lifestyle parameters seem to be as important as cardiovascular history, gender or educational level. Furthermore, HRQoL was significantly associated with certain cardiovascular risk factors in those patients being medically treated (Table 4). Regarding blood pressure the associations with the different HRQoL measures were found to be non-significant or to go in the opposite direction, with worse HRQoL being associated with better blood pressure values. Regarding total cholesterol a significant association was seen with MCS-12. No significant relation was found with LDL-C and fasting glucose, whereas HbA1c was significantly associated with all HRQoL measures in patients with diabetes.

Table 1: Patient characteristics at the time of the interview (n=8734)

	Men (n=6516)	Women (n=2218)	All (n=8734)
Age in years, Mean (SD)	62.3 (9.5)	65.9 (8.9)	63.2 (9.5)
Age categories			
<50 years	10.6% (688/6516)	5.0% (112/2218)	9.16% (800/8734)
50-59 years	29.5% (1924/6516)	19.9% (442/2218)	27.1% (2366/8734)
60-69 years	37.4% (2440/6516)	40.1% (890/2218)	38.1% (3330/8734)
≥70 years	22.5% (1464/6516)	34.9% (774/2218)	25.6% (2238/8734)
Recruiting Diagnosis			
CABG	20.5% (1339/6516)	17.1% (379/2218)	19.7% (1718/8734)
PTCA	43.1% (2806/6516)	35.3% (782/2218)	41.1% (3558/8734)
AMI	19.2% (1248/6516)	20.7% (459/2218)	19.5% (1707/8734)
Ischemia	17.2% (1123/6516)	27.0% (598/2218)	19.7% (1721/8734)
Education			
Primary education	22.5% (1456/6480)	33.4% (737/2207)	25.2% (2193/8687)
Secondary education	57.3% (3714/6480)	54.9% (1211/2207)	56.7% (4925/8687)
High education	20.2% (1310/6480)	11.7% (259/2207)	18.1% (1569/8687)
Diabetes	22.6% (1459/6454)	29.8% (657/2203)	24.4% (2116/8657)
Raised fasting glucose	90.7% (943/1040)	87.4% (396/453)	89.7% (1339/1493)
Raised HbA1c	60.9% (592/972)	73.8% (321/435)	64.9% (913/1407)
History of stroke	4.1% (268/6500)	5.7% (127/2212)	4.53% (395/8712)
Recurrent CHD after recruiting diagnosis	14.1% (912/6483)	11.4% (251/2204)	13.4% (1163/8687)
Central obesity	45.7% (2940/6433)	73.4% (1609/2193)	52.7% (4549/8626)
Current smoker	19.0% (1234/6500)	10.9% (242/2214)	16.9% (1476/8714)
Low physical activity	63.9% (3880/6073)	72.8% (1483/2038)	66.1% (5363/8111)
Raised total cholesterol	47.7% (2936/6155)	62.0% (1309/2111)	51.4% (4245/8266)
On lipid lowering medication (LLM)	80.3% (5210/6487)	77.9% (1718/2205)	79.7% (6928/8692)
Raised total cholesterol in treated patients	41.4% (2035/4912)	56.8% (929/1637)	45.3% (2964/6549)
Raised LDL-cholesterol	52.6% (2511/4770)	61.3% (980/1598)	54.8% (3491/6368)
Raised LDL-cholesterol in patients on LLM	46.5% (1797/3865)	55.0% (570/1267)	48.6% (2638/5132)
Raised Blood pressure	54.5% (3544/6503)	60.8% (1347/2215)	56.1% (4891/8718)
On antihypertensive medication	67.1% (4350/6481)	80.3% (1778/2215)	70.5% (6928/8692)
Raised Blood Pressure in medically patients	61.4% (2665/4341)	66.3% (1176/1775)	62.8% (3841/6116)

Figure 1: Crude mean HRQoL outcomes across EUROASPIRE III countries



* Adjusted for age, gender, educational level, recruiting diagnosis, diabetes, history of stroke and recurring events (p<0.001)

Table 2: Association between patient characteristics and different HRQoL instruments (Mean (SD))

	PCS-12	MCS-12	EQ-VAS
All	42.14 (10.15)	49.15 (10.22)	66.42 (18.84)
Gender			
Male	43.20 (10.02)	49.93 (9.96)	67.85 (18.59)
Female	38.82 (9.84)	46.75 (10.64)	62.22 (18.84)
	p<0.001*	p<0.001	p<0.001
Age			
< 50 yrs	45.59 (9.96)	48.84 (10.51)	71.43 (18.18)
50-59 yrs	43.31 (10.1)	48.94 (10.22)	67.48 (18.73)
60-69 yrs	42.16 (9.99)	49.57 (10.19)	66.72 (18.66)
≥ 70 yrs	39.56 (9.89)	48.90 (10.13)	63.03 (18.9)
	p<0.001	p=0.034	p<0.001
Recruiting diagnosis			
CABG	42.53 (10.03)	50.23 (9.88)	66.85 (19.43)
PTCA	43.03 (10.06)	49.27 (10.18)	67.92 (18.5)
AMI	41.83 (10.13)	48.58 (10.24)	65.64 (18.56)
ISCHAEMIA	40.04 (10.18)	48.47 (10.53)	63.63 (18.88)
	p<0.001	p=0.214	p=0.011
Educational level			
Primary	40.95 (10.36)	47.98 (10.89)	64.87 (20)
Secondary	41.95 (10.04)	49.27 (10.08)	66.44 (18.55)
High	44.28 (9.88)	50.44 (9.53)	68.32 (18)
	p<0.001	p<0.001	p<0.001
Diabetes			
No	42.94 (9.97)	49.48 (10.03)	67.34 (18.57)
Yes	39.46 (10.27)	48.10 (10.76)	63.50 (19.43)
	p<0.001	p<0.001	p<0.001
Central Obesity			
No	43.53 (9.98)	49.67 (9.96)	68.33 (18.45)
Yes	40.87 (10.11)	48.73 (10.44)	64.76 (18.99)
	p<0.001	p=0.199	p<0.001
Smoking			
No	42.04 (10.14)	49.37 (10.00)	66.56 (18.71)
Yes	42.64 (10.17)	48.06 (11.18)	65.71 (19.40)
	p=0.001	p<0.001	p<0.001
Physical activity			
<20min, 3x/week	40.79 (10.19)	48.69 (10.39)	64.39 (19.12)
≥20 min, 3x/week	45.52 (9.28)	50.54 (9.58)	71.08 (17.22)
	p<0.001	p<0.001	p<0.001
History of stroke			
No	42.39 (10.08)	49.24 (10.16)	66.80 (18.77)
Yes	36.92 (10.42)	47.17 (11.3)	58.43 (18.83)
	p<0.001	p=0.001	p<0.001
Recurring coronary event after IE			
No	42.34 (10.13)	49.26 (10.15)	66.76 (18.85)
Yes	40.90 (10.19)	48.47 (10.59)	64.25 (18.64)
	p<0.001	p=0.109	p<0.001

*p-value adjusted for age, gender, educational level

Table 4: Association between uncontrolled cardiovascular risk factors different HRQoL instruments (mean (SE))

	PCS-12	MCS-12	EQ-VAS
Raised blood pressure in treated patients			
No	38.24 (0.80)*	47.04 (0.73)	62.17 (1.38)
Yes	39.28 (0.78)	47.65 (0.71)	63.01 (1.35)
	p<0.001**	p=0.040	p=0.099
Raised total cholesterol in treated patients			
No	39.35 (0.79)	47.90 (0.71)	63.84 (1.42)
Yes	39.11 (0.79)	47.22 (0.72)	62.96 (1.43)
	p=0.329	p=0.011	p=0.056
Raised LDL-cholesterol in treated patients			
No	39.40 (0.84)	47.30 (0.74)	63.08 (1.50)
Yes	39.43 (0.84)	46.82 (0.74)	62.65 (1.50)
	p=0.909	p=0.104	p=0.408
Raised fasting glucose in diabetes patients			
No	37.75 (1.33)	44.50 (1.26)	58.43 (2.34)
Yes	37.58 (1.10)	45.05 (0.95)	58.83 (1.84)
	p=0.839	p=0.559	p=0.809
Raised HbA1c in diabetes patients			
No	39.01 (1.18)	47.43 (1.17)	61.90 (2.04)
Yes	37.55 (1.13)	45.62 (1.10)	59.15 (1.92)
	p=0.013	p=0.006	p=0.013

*adjusted mean
**p-value adjusted for age, gender, educational level, recruiting diagnosis, diabetes, history of stroke and coronary recurring events

Looking at the number of CVD risk factors (blood pressure, total cholesterol, smoking, physical activity, central obesity) revealed that an increase in the amount of risk factors was associated with a gradual decrease in HRQoL even after adjustment for patient characteristics (Table 5). Fitting a multiple linear model showed that each additional risk factor was associated with a 0.872 (p<0.001) decrease in PCS-12, a 0.326 (p=0.002) decrease in MCS-12 and a 1.368 (p<0.001) decrease on the EQ-VAS.

Table 5: HRQoL means (SD) in relation to the number of risk factors

Number of risk factors	PCS-12	MCS-12	EQVAS
0	46.11 (9.76)	50.80 (9.22)	72.85 (17.23)
1	44.38 (9.79)	50.01 (9.62)	70.25 (18.07)
2	42.15 (10.16)	49.49 (10.16)	66.68 (18.44)
3	41.27 (10.07)	48.62 (10.33)	64.82 (18.90)
4	39.73 (9.88)	47.98 (10.76)	61.99 (19.64)
5	38.21 (9.73)	46.85 (12.37)	60.47 (18.06)
p-value	<0.001*	0.023	<0.001

*p-value adjusted for age, gender, educational level, recruiting diagnosis, diabetes, history of stroke and recurring coronary events.Risk factors included are: raised blood pressure, raised total cholesterol, current smoking, low physical activity and central obesity.

Table 3: Results of multilevel linear regression analyses for the association between patient characteristics and HRQOL

	PCS-12		MCS-12		EQ-VAS	
Patient characteristics	***β (SE)****	***p-value***	***β (SE)****	***p-value***	***β (SE)****	***p-value***
Intercept	56.709 (1.033)	<0.001	50.347 (1.016)	<0.001	84.60 (1.88)	<0.001
Age	-0.153 (0.012)	<0.001	0.011 (0.013)	0.407	-0.183 (0.023)	<0.001
Gender						
Male	Reference		Reference		Reference	
Female	-2.154 (0.267)	<0.001	-2.749 (0.289)	<0.001	-2.878 (0.499)	<0.001
Educational level						
Primary education	-0.971 (0.293)	0.001	-0.570 (0.315)	0.071	-2.046 (0.549)	<0.001
Secondary education	Reference		Reference		Reference	
High education	2.231 (0.296)	<0.001	1.144 (0.320)	<0.001	2.635 (0.558)	<0.001
Recruiting diagnosis						
CABG	0.518 (0.305)	0.090	0.604 (0.329)	0.067	0.999 (0.574)	0.082
PTCA	Reference		Reference		Reference	
AMI	0.115 (0.315)	0.714	0.681 (0.339)	0.045	1.677 (0.606)	0.006
Ischemia	-1.588 (0.337)	<0.001	0.282 (0.363)	0.436	-0.210 (0.629)	0.739
Diabetes						
No	Reference		Reference		Reference	
Yes	-2.535 (0.261)	<0.001	-1.160 (0.281)	<0.001	-2.911 (0.486)	<0.001
History of stroke						
No	Reference		Reference		Reference	
Yes	-3.591 (0.520)	<0.001	-1.456 (0.561)	0.009	-5.426 (0.979)	<0.001
Recurrent coronary event after recruiting diagnosis						
No	Reference		Reference		Reference	
Yes	-1.688 (0.319)	<0.001	-0.580 (0.344)	0.093	-2.251 (0.604)	<0.001
Smoking						
No	Reference		Reference		Reference	
Yes	-0.917 (0.301)	0.002	-1.622 (0.325)	<0.001	-2.062 (0.570)	<0.001
Physical activity						
≥20 min, 3x/week	Reference		Reference		Reference	
<20min, 3x/week	-3.094 (0.243)	<0.001	-1.121 (0.262)	<0.001	-4.384 (0.456)	<0.001
Central obesity						
No	Reference		Reference		Reference	
Yes	-1.528 (0.228)	<0.001	0.042 (0.246)	0.865	-1.887 (0.432)	<0.001

4. Discussion

In this study, including 8734 stabilized CHD patients from 22 European countries, we aimed to analyse the association between HRQoL and patient characteristics. As expected the overall HRQoL scores in our cohort of CHD patients were lower compared to the general population (König et al, 2009) and similar to previously reported results (Xie et al, 2008). Our analyses revealed that patient characteristics were significantly associated with HRQoL. Firstly, patients from Eastern European countries were more likely to have an impaired HRQoL. Similar findings have been previously reported in the general population with lower overall subjective well-being scores in less prosperous countries (The EuroQol Group's International Task Force on Self-Reported Health, 2004). Secondly, in accordance with the literature, CHD women reported lower HRQoL results than men (Agewall et al, 2004; Brink et al, 2005; Duenas et al, 2011; Emery et al, 2004; Phillips-Bute et al, 2003; Pragodpol et al, 2012; Schweikert et al, 2006; Xie et al, 2008), an observation which was also seen in the general population (Franco et al, 2012; Xie et al, 2008). With regard to age, a significant association – with younger patients reporting a better HRQoL – was observed with the PCS-12 and the EQ-VAS. Likewise other research groups found higher HRQoL values in younger CHD patients (Brink et al, 2005; Lee et al, 2012; Pragodpol et al, 2012; Schweikert et al, 2006). Xie and colleagues reported similar results regarding the physical score; however, for the mental score and the EQ-5D, better values were found in older CHD patients (Xie et al, 2008). Patients with self-reported diabetes were more likely to have a worse HRQoL. Similarly Xie et al. reported significantly lower HRQoL outcomes on both the SF-12 and the EQ-5D in these patients whereas Peterson et al. reported a 3 point lower score on PCS-12 in patients with diabetes (Peterson et al, 2006; Xie et al, 2008). In addition, similar to the results reported by Lee et al., lower educated patients had significantly lower HRQoL outcomes (Lee et al, 2012). Analyses also revealed significantly higher HRQoL scores in patients undergoing revascularization as recruiting diagnosis, confirming previous studies (Kim et al, 2005; Lukkarinen et al, 2006; Sevinc et al, 2010; Weintraub et al, 2008). Other significant predictors of impaired HRQoL were: having a history of stroke or suffering from a recurring coronary event. Several studies have shown a negative influence of stroke on HRQoL (Leach et al, 2011; Paul et al, 2005; Saarni et al, 2006; Schwander et al, 2009; Xie et al, 2008). Recurring cardiovascular events are also known to cause a decrease in HRQoL, although to a smaller extent than the HRQoL reduction associated with initial events (Schwander et al, 2009). Lifestyle risk factors were significantly associated with HRQoL. In line with the literature, central obesity was associated with a decrease in HRQoL (Jarvinen et al, 2007; Lee et al, 2012; Oreopoulos et al, 2010). In addition, we found an association between HRQoL and physical activity, with better HRQoL outcomes in physically active persons. Similarly, Sevinç et al. reported a higher HRQoL in coronary patients who are active or exercise regularly, compared to sedentary patients (Sevinc et al, 2010). Finally, a significant association between HRQoL and current smoking was seen (Haddock et al, 2003; Taira et al, 2000). In contrast to some authors stating that smoking cessation does not improve HRQoL significantly, we have found significantly higher HRQoL in quitters, similar to non-smokers (data not shown) (Hoogwegt et al, 2010; Quist-Paulsen et al, 2006; Wiggers et al, 2006). These results stress the importance of promoting healthy lifestyle changes in coronary patients, not only to prevent recurrent events but also to increase patients' HRQoL. Our findings are in line with the latest European recommendations on CVD prevention, promoting multimodal, behavioural interventions in CHD patients (Perk et al, 2012). The interventions should include promotion of healthy lifestyle based on cognitive–behavioural strategies, through behavioural change including nutrition, exercise, smoking cessation, coping with the illness and improving medication adherence. When looking at the relation between HRQoL and CVD risk factors in patients being treated, less pronounced differences were seen across different risk groups. A negative association was found between SF-12 and raised blood pressure, which was eliminated after adjustment for medication intake. Indeed about 28% of the EUROASPIRE III patients were taking nitrates and 30% were taking diuretics at the time of the interview, medications which are often given in patients with angina and heart failure respectively, two conditions that are associated with a substantial decrease in HRQoL (Herlitz et al, 2005; Pragodpol et al, 2012). Some previous studies did find a correlation between HRQoL and blood pressure, with worse HRQoL in hypertensive patients whereas others did not find any association (Carvalho et al, 2012; Herlitz et al, 2005; Sevinc et al, 2010; Soini et al, 2010). Uncontrolled total cholesterol was significantly associated with a worse MCS-12, whereas no association was found with LDL-cholesterol. Similarly, Sevinç et al. found no significant association between HRQoL and cholesterol (Sevinc et al, 2010). HbA1c but not fasting glucose was significantly associated with HRQoL with worse health outcomes in those with a lower HRQoL. The latter observation was in accordance with published literature (Lee et al, 2012). Khanna et al. found a significant association between HbA1c and diabetes-specific HRQoL whereas Lau et al. only found an effect on the mental score of SF-12 (Khanna et al, 2012; Lau et al, 2004). Furthermore, in accordance with the literature, the number of risk factors was inversely associated with HRQoL (Li et al, 2008). These results reaffirm the high importance of a holistic approach regarding risk factor prevention. Overall, the greatest association was seen with physical functioning. This is in line with the review by Smith et al. (1999) stating that physical health has a much greater impact on health status than mental health. Our analyses did not include the $EQ\text{-}5D_{index}$ since country-specific weights to calculate the $EQ\text{-}5D_{index}$ were not available for all 22 countries. However, when performing the analyses using the UK weights for all the countries, similar results as reported were found (data not shown). The EUROASPIRE III study is one of the largest surveys throughout Europe assessing patients' subjective HRQoL in a stable coronary population. Data collection was organized in a standardized way and HRQoL was measured by means of 2 different widely used HRQoL instruments. In order to account for HRQoL differences inherent to the centre, multilevel analyses were used. The major limitation of our study is its cross-sectional design; therefore no statement about causality, only about the association between HRQoL and different characteristics, can be made. Furthermore, results should be interpreted with caution since most of the data were self-reported. Additionally, results are not country representative as the survey was carried out in selected geographical areas in each country. In conclusion, patient characteristics such as age, gender, educational level, physical activity, smoking status, central obesity and comorbidities seem to be significantly associated with HRQoL in coronary patients. In addition HRQoL, especially the physical health components and the EQ-VAS, seems to decrease significantly with an increasing number of risk factors.

Chapter 6.
Association HRQoL/psychological distress and lifestyle changes in coronary patients

Based on:

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The association between self-reported lifestyle changes and health-related quality of life in coronary patients: the EUROASPIRE III survey

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Abstract

Background: Patients with coronary heart disease often suffer from an impaired health-related quality of life (HRQoL) and psychological distress. A healthier lifestyle not only extends individuals' lengths of life but might also improve their HRQoL/psychological distress. The aim of this study was to explore the relation between self-reported lifestyle changes and HRQoL/psychological distress in European coronary patients.

Methods: Data on 8745 coronary patients, from 22 countries, participating in the EUROASPIRE III survey (2006–2007) were used. These patients hospitalized for coronary artery bypass graft, percutaneous coronary intervention, acute myocardial infarction, or myocardial ischemia were interviewed and examined at least 6 months and no later than 3 years after their hospital admission to gather information on their EQ-5D, SF-12, HADS, self-reported lifestyle changes, and risk factors.

Results: Significantly better HRQoL/psychological distress scores were found in ex-smokers compared to current smokers. Patients who made an attempt to increase their physical activity level had a better HRQoL/psychological distress compared to those who had not made an attempt. Furthermore dietary changes were associated with HRQoL/psychological distress, with better outcomes in patients who tried to reduce fat and salt intake and increase fish, fruit, and vegetable intake. The intention to change behaviour was not associated with HRQoL/psychological distress.

Conclusions: Better HRQoL/psychological distress scores were found in those coronary patients who adopted a healthier lifestyle. The actual lifestyle changes – smoking cessation, increasing physical activity, and adopting a healthy diet – and not the intention to change are associated with better HRQoL/psychological distress outcomes.

1. Introduction

Even though cardiovascular disease (CVD) mortality rates have fallen rapidly in many European countries in the latest decades, CVD continues to be the number one cause of morbidity and mortality (Nichols et al, 2012; Perk et al, 2012). Many risk factors contribute to the development of CVD. In addition to unchangeable risk factors such as age, family history, gender, and geographical area, the progress of CVD is driven by several modifiable risk factors (Yusuf et al, 2004). Unhealthy lifestyle habits such as smoking, physical inactivity, and unhealthy eating habits have a major influence on the development of CVD; hence, guidelines on CVD prevention have stressed the importance of adopting a healthy lifestyle both in high-risk patients as well as in CVD patients (Pearson et al, 2002; Perk et al, 2012; Vanhees et al, 2012; World Health Organisation, 2007). According to several studies in the general population, the uptake of a healthier lifestyle – such as ceasing smoking, becoming physically active, and developing healthy eating habits – will not only extend the length of life but also improve the health-related quality of life (HRQoL) (Anokye et al, 2012; Henriquez Sánchez et al, 2012; Piper et al, 2012). HRQoL is a comprehensive concept referring to the individual’s physical, emotional, and social wellbeing (Thompson et al, 2003). Coronary patients often suffer from an impaired HRQoL; hence, many of them consider HRQoL equally important as the length of life. Patients and their caregivers as well as policy makers have a particular interest in finding ways to improve patients’ overall wellbeing (Thompson et al, 2003). However, evidence regarding the direct association between lifestyle changes and HRQoL or psychological well-being in coronary patients is scarce. Some studies report on the association with smoking cessation, weight loss, or physical activity; however, to our knowledge, no study has investigated the association of lifestyle changes in coronary patients with various HRQoL/psychological distress measures in a systematic manner (Haddock et al, 2003; Oreopoulos et al, 2010; Quist-Paulsen et al, 2006; Schweikert et al, 2009; Sevinc et al, 2010; Taira et al, 2000). The aim of our study was to explore the relation between several self-reported lifestyle changes and HRQoL/psychological distress in coronary patients using data from a large European cohort. Knowledge about this association may lead to an increased motivation in patients to change their behaviour. Moreover, the outcomes of this study can be important for decision makers in defining priorities related to their prevention policy. We hypothesized that coronary patients who have not made an attempt to change their behaviour in order to adopt a healthier lifestyle would have worse HRQoL/psychological distress.

2. Methods

Study population and data collection

This study is based on data collected during the EUROASPIRE III survey (European Action on Secondary and Primary Prevention through Intervention to Reduce Events). Details of the study have been described extensively elsewhere (Kotseva et al, 2009b). Briefly, the EUROASPIRE III survey, conducted during 2006–07 under the auspices of the European Society of Cardiology Euro Heart Survey Programme, was a cross-sectional study to determine whether the European recommendations on CVD prevention were being followed in everyday clinical practice across 22 European countries (76 hospital centres): Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, Romania, Russian Federation, Slovenia, Spain, The Netherlands, Turkey, and the UK. Patients aged between 18 and 80 years, hospitalized for coronary artery bypass graft, percutaneous coronary intervention, acute myocardial infarction, or myocardial ischemia but without evidence of myocardial infarction – hereafter referred to as the recruiting diagnosis – were retrospectively identified from diagnostic registers, hospital discharge lists or other sources. In total, 8966 patients (participation rate 73%) were interviewed and examined at least 6 months and no later than 3 years after their initial hospital admission. The present study included only those patients for which HRQoL/psychological distress information was available (n=8745). Data collection was conducted by trained research staff using standardized methods and instruments. Patient medical records from the initial hospital admission were reviewed, to collect – among others – information on their initial diagnosis, waist circumference, body weight, and height. At the time of interview and examination (median time= 1.24 years after the recruiting diagnosis), physical measurements were performed in light indoor clothes without shoes using calibrated measuring equipment. In addition, information was obtained on risk factors and adopted lifestyle changes. During the interview, data were gathered on smoking history and smoking cessation attempts undertaken since the initial hospital admission. Likewise, information on dietary steps (reducing salt intake, reducing fat intake, increasing fish intake, increasing fruit and vegetable intake) taken since the initial hospital admission to eat healthier and to reduce their body weight were collected. Additionally, several questions were asked regarding patients' physical activity level and the attempts undertaken to increase their physical activity level. Patient were asked to describe their self-perceived physical activity level on the following scale: no physical activity; light physical activity; vigorous physical activity for 20 minutes, 2 or 3 times a week; or vigorous physical activity for 20 minutes ≥3 times a week. Furthermore, they completed the short form International Physical Activity Questionnaire (IPAQ) allowing the categorization of patients according to their physical activity score. In addition, information about their future intention to change was gathered. The questions as asked during the interview can be found in the Appendix. Body mass index (BMI) was calculated as the patient's weight in kilograms divided by the squared height in meters. The WHO classes were used for classification: normal range was defined as BMI <24.9 kg/m^2; overweight was defined as BMI 25–29.9 kg/m^2, and obesity as BMI ≥30 kg/m^2 (World Health Organization, 1995). Central obesity was defined as waist circumference 102 cm in men and 88 cm in women (Lean et al, 1995). Smokers were those who reported to be a current smoker or who had a carbon monoxide in breath value exceeding 10 ppm at the time of the interview. IPAQ classes were calculated according to the guidelines for data processing and analysis (IPAQ core group, 2005). A low IPAQ score was defined as no activity or some activity reported but not enough to meet the other categories. A moderate IPAQ score was defined as 3 or more days of vigorous-intensity activity of at least 20 minutes per day, or 5 or more days of moderate intensity activity and/or walking of at least 30 minutes per day, or 5 or more days of any combination of walking, moderate-intensity, or vigorous-intensity activities achieving a minimum total physical activity of at least 600 MET-minutes/week. Metabolic equivalent

(MET) is a common outcome measure used to express the energetic expenditure of different physical activities (Ainsworth et al, 2000). A high IPAQ score was defined as vigorous-intensity activity on at least 3 days and accumulating at least 1500 MET-minutes/week or 7 or more days of any combination of walking, moderate- or vigorous- intensity activities accumulating at least 3000 MET-minutes/ week. To assess patients' HRQoL/psychological distress, three self-administered questionnaires were given to the patients during the interview: the EuroQoL-5D (EQ-5D), the 12-item short form health survey (SF-12), and the Hospital Anxiety and Depression Scale (HADS). The former two are health status measures, whereas the latter assesses psychological well-being. Questionnaires were administered in the countries' official language. Validity of these scales in this sample has been reported previously (De Smedt et al, 2013b). The EQ-5D contains a self-classifier using five dimensions, with three response categories each, to assess patients' health status: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; from which an EQ-5D$_{index}$ score can be calculated (with 1 representing perfect health, 0 representing death, and <0 representing a health state perceived worse than death). In addition, patients were asked to indicate their current health status on a visual analogue scale (EQ-VAS) ranging from 0 (worst imaginable) to 100 (best imaginable) (Rabin et al, 2001). The current analysis only makes use of the VAS, as the normality assumptions for the EQ-5D$_{index}$ were not met. The SF-12 is a shortened version of the SF-36 consisting of 12 Likert scale questions, covering eight dimensions: general health, physical functioning, role physical, bodily pain, vitality, social functioning, role emotional, and mental health. Both physical (PCS-12) and mental functioning (MCS-12) component scores, ranging between 0 and 100, were calculated using a common scoring algorithm, with lower scores representing worse and higher scores representing better health (Ware et al, 2002). The SF-12 was not administered in Hungary. The HADS contains seven items related to anxiety and seven to depression, each with a 4-point response scale. Item scores can be added to obtain the summary scores on anxiety (HADS-A) and depression (HADS-D) separately. The total score on each subscale ranges between 0 and 21 with higher scores representing worse outcomes (Zigmond et al, 1983).

Statistical analysis

All analyses are based on generalized linear mixed models in order to account for the clustering of patients within countries. HRQoL differences between groups were tested using multiple linear regression models. Potential confounding caused by differences in age, gender, diagnostic category, education, cardiovascular history, and diabetes was adjusted for all models. Results are shown for men and women together, since the interaction term with the different items was non-significant. Significance levels were set at p <0.05. All statistical analyses were performed using the IBM SPSS statistical software (version 20.0).

3. Results

The main characteristics of the patients included are shown in Table 1. Data on 6523 men (74.6%) and 2222 women (25.4%) were available for analysis. Patients' age (mean ± SD) was 63.2 ± 9.5 years. At the time of the recruiting diagnosis, patients' BMI was 28.3 ± 4.4 kg/m2, 30.5% of patients were obese, 44.9% were central obese, and 30.2% reported smoking. At the time of the interview, patients' BMI was 28.9 ± 4.5 kg/m2, 35.4% were obese, 16.9% were still smoking, and 11.7% reported no physical activity. In those patients being overweight or obese at the time of the recruiting diagnosis, 77.0 % reported ever being offered weight advice by a doctor or health professional, 68.2% of all patients reported having ever received personal advice on increasing physical activity, 92.0% had been ever advised on a healthy diet, and 87.7% of patients smoking at the time of the recruiting diagnosis had been ever offered smoking advice. Since the recruiting diagnosis, 81.8% of smokers made an attempt to quit smoking in order to reduce their risk of recurrent coronary heart disease, 90.2% of patients tried to eat healthier by reducing salt, sugar, or fat intake and increasing fish, fruit, and vegetable intake, and 58.6% of patients took steps to increase their physical activity level.

Smoking

HRQoL scores were significantly worse in smokers compared to non-smokers, with ex-smokers (both patients who stopped smoking before or after the recruiting diagnosis) having HRQoL values leaning towards the scores of never smokers (Table 2). Patients who had made an attempt to quit smoking since the recruiting diagnosis, had a better HRQoL score (HADS-D, EQ-VAS, PCS-12) compared to those who did not undertake an attempt to quit. However, as can bee seen from Table 2 the smoking status at the time of interview was responsible for these HRQoL differences. Indeed, whether or not a cessation attempt was made had no impact on the HRQoL outcomes in those still smoking at the time of the interview. A closer look into the quitters' HRQoL indicated that the time since smoking cessation (<6 months vs. >6 months) did not have an influence on their self-perceived mental, physical, and overall wellbeing. Patients still smoking at the interview, who had the intention to quit smoking in the following 6 months did not differ in HRQoL scores from those who did not consider smoking cessation.

Physical activity

A better HRQoL was reported in patients who had made an attempt to increase their physical activity compared to those who had not made such an attempt (Table 3). The actual physical activity level reported during the interview was significantly associated with HRQoL. A positive relation between HRQoL outcomes and the amount of exercise was seen both with the results of the validated IPAQ instrument as well as with the results of a single question, asking about the patients' self-perceived physical activity level.

Table 1: Patient characteristics

	Men (n=6523)	Women (n=2222)	All (n=8745)
Age in years, Mean (SD)	62.3(9.5)	65.9(8.9)	63.2(9.5)
Recruiting Diagnosis (%)			
CABG	20.6%(1343/6523)	17.1%(380/2222)	19.7%(1723/8745)
PTCA	43.1%(2809/6523)	35.3%(784/2222)	41.1%(3593/8745)
AMI	19.1%(1248/6523)	20.7%(460/2222)	19.5%(1708/8745)
Ischemia	17.2%(1123/6523)	26.9%(598/2222)	19.7%(1721/8745)
Education (%)			
Primary education	22.5%(1459/6487)	33.5%(740/2211)	25.3%(2199/8698)
Secondary education	57.3%(3717/6487)	54.8%(1212/2211)	56.7%(4929/8698)
High education	20.2%(1311/6487)	11.7%(259/2211)	18.1%(1570/8698)
Diabetes (%)	22.6%(1461/6461)	29.9%(659/2207)	24.5%(2120/8668)
History of stroke (%)	4.1%(268/6507)	5.7%(127/2216)	4.5%(395/8723)
Recurrent CHD after recruiting diagnosis (%)	14.1%(912/6490)	11.4%(251/2208)	13.4%(1163/8698)
At time of recruiting diagnosis			
BMI, Mean (SD)	28.2(4.2)	28.87(4.84)	28.3(4.4)
Obesity (%)	28.5%(789/2764)	36.1%(352/974)	30.5%(1141/3738)
Central obesity (%)	38.6%(468/1211)	61.3%(284/463)	44.9%(752/1674)
Smoking (%)	33.8%(2201/6508)	19.6%(434/2215)	30.2%(2635/8723)
At time of interview			
BMI, Mean (SD)	28.6(4.2)	29.70(5.19)	28.9(4.5)
Obesity (%)	32.2%(2093/6500)	44.8%(990/2210)	35.4%(3083/8710)
Central obesity (%)	41.6%(2681/6440)	70.4%(1546/2196)	48.9%(4227/8636)
Smoking (%)	19%(1236/6507)	10.9%(242/2218)	16.9%(1478/8725)
Self-reported PA			
No PA weekly (%)	10.8%(696/6428)	14.4%(316/2193)	11.7%(1012/8621)
Light PA in most weeks (%)	56.3%(3618/6428)	63.0%(1381/2193)	58.0%(4999/8621)
Vigorous PA, ≥20 min, once or twice/week (%)	17.5%(1122/6428)	13.3%(291/2193)	16.4%(1413/8621)
Vigorous PA, ≥20 min, ≥3 times a week (%)	15.4%(992/6428)	9.3%(205/2193)	13.9%(1197/8621)
IPAQ moderate/high (%)			
Low	22.3%(774/3476)	31.9%(360/1129)	24.6%(1134/4605)
Moderate	38.8% (1350/3476)	39.1%(442/1129)	38.9% (1792/4605)
high	38.9%(1352/3476)	29.0%(327/1129)	36.5% (1679/4605)
Lifestyle advice on (%)			
Smoking cessation (in prior smokers)	88.3%(1935/2191)	84.5%(364/431)	87.7%(2299/2622)
Diet	92.4%(5989/6479)	90.9%(2011/2213)	92.0%(8000/8692)
Weight (if prior BMI>25)	75.7%(1607/2122)	80.5%(616/765)	77.0%(2223/2887)
Physical activity	69.2%(4467/6457)	65.3%(1439/2204)	68.2%(5906/8661)
Lifestyle changes to reduce risk of heart disease (%)			
Trying to stop smoking (in prior smokers)	81.2%(1713/2110)	84.9%(348/410)	81.8%(2061/2520)
Trying to eat healthier	89.7%(5645/6291)	91.6%(1963/2143)	90.2%(7608/8434)
Trying to increase physical activity	59.9%(3792/6327)	54.9% (1175/2142)	58.6%(4967/8469)
HRQoL/psychological distress at interview, Mean (SD)			
HADS-A	5.48(3.80)	7.24(4.16)	5.93(4.0)
HADS-D	4.75(3.54)	6.01(3.86)	5.07(3.67)
EQ-5D$_{index}$	0.78(0.23)	0.69(0.25)	0.76(0.24)
EQ-VAS	67.85(18.59)	62.22(18.94)	66.42(18.84)
PCS-12	43.20(10.02)	38.82(9.84)	42.14(10.15)
MCS-12	49.93(9.96)	46.75(10.64)	49.15(10.22)

A combined parameter including IPAQ class and increasing physical activity revealed significant differences across groups, with the lowest HRQoL reported in patients in the lowest IPAQ class who have not made any attempt to become physically active, whereas those having a moderate or high IPAQ level who declared to have made an attempt to increase their physical activity reported the highest HRQoL.

At interview, in patients with a normal weight not yet exercising regularly, no significant difference was found in HRQoL (except for PCS-12) between those willing to become physically active, versus those not willing to become physically active. In contrast, patients being overweight or obese at interview with the intention to exercise regularly in the near future reported a higher HRQoL compared to those with no intention to become regularly physically active.

Body weight and healthy diet

BMI was significantly associated with HRQoL, with obese patients having inferior HRQoL outcomes (Table 4). At interview, among patients who were still overweight or obese, those with the intention to lose weight in the upcoming months did not differ significantly in HRQoL (except for PCS-12) from those who did not have any intention to lose weight. With regard to actual weight change, no significant difference was found in HRQoL outcomes (except for PCS-12) between those who had lost weight (5% weight loss), maintained their weight level (± 5% weight change), or gained weight (5% weight gain) between the recruiting diagnosis and the interview. HRQoL differed significantly between those who had taken steps to adopt a healthier diet, compared to those who did not. Patients reducing fat intake, reducing salt intake, increasing fish intake, or increasing fruit and vegetable intake had higher HRQoL values; however, the effects on the psychological dimensions was sometimes non significant (MCS-12, HADS-A).

4. Discussion

The aim of the current study was to investigate the relationship between self-reported lifestyle changes and HRQoL in coronary patients, using a large cohort originating from 22 European countries. Higher HRQoL scores were found in coronary patients who adopted a healthier lifestyle – by ceasing smoking, developing healthier eating habits, or increasing their physical activity – even after adjustment for other patient characteristics. Furthermore, no significant differences were found in HRQoL outcomes between patients considering smoking cessation versus those not intending to quit. It is thus unlikely that those willing to quit smoking had a higher initial HRQoL allowing them to find the motivation to quit. Nonetheless, it remains possible that ex-smokers differ from current smokers in several unmeasured characteristics, so these results should be interpreted with caution. In patients with a normal body weight, no differences were found between those intending to become more regularly physically active versus those without this intention. Likewise, overweight and obese patients considering weight loss did not differ in HRQoL compared with the non-intenders (except PCS-12), whereas overweight and obese patients intending to become physically active reported a higher HRQoL compared to those without this intention. Not surprisingly, the greatest HRQoL differences were found in the items capturing the current physical health status (PCS-12). After all, physical activity constitutes a component of HRQoL. Patients experiencing problems with their physical health, due to pain/discomfort for instance, may be less likely to become physically active.

Table 2: Association between HRQoL and SMOKING CESSATION

	HADS-A	HADS-D	EQ-VAS	PCS-12	MCS-12
COMPLETE SAMPLE					
Smoking history†					
Ever smoker (n=3058)	6.72 ± 0.22	5.68± 0.22	62.62± 1.36	38.52± 0.78	47.99± 0.67
Prior smoker (n=1279)	6.73± 0.24	5.78± 0.24	62.26± 1.41	38.77± 0.81	48.05± 0.71
Smoker (n=1478)	7.21± 0.24	6.48± 0.24	60.73± 1.41	37.81± 0.80	46.32± 0.71
Never smoker (n=2896)	6.70± 0.22	5.85± 0.22	63.68± 1.35	39.58± 0.77	47.37± 0.67
	p<0.000	**p<0.001**	**p=0.003**	**p<0.001**	**p<0.001**
SMOKING AT TIME OF RECRUITING DIAGNOSIS					
Smoking cessation attempt					
Yes (n=2061)	7.01± 0.34	6.12± 0.31	62.11± 1.64	39.89± 0.96	46.84± 0.93
No (n=459)	7.30± 0.38	6.54± 0.34	59.77± 1.83	38.41± 1.05	45.75± 1.03
	p=0.160	**p=0.030**	**p=0.018**	**p=0.004**	p=0.054
Smoking status at interview					
Still smoking – no cessation attempt (n=376)	7.32± 0.38	6.65± 0.35	60.61± 1.85	38.59± 1.07	45.38± 1.05
Still smoking – cessation attempt (n=915)	7.38± 0.34	6.54± 0.31	60.91± 1.68	39.22± 0.99	45.69± 0.95
Prior smoker† (n=1279)	6.83± 0.34	5.83± 0.31	62.22± 1.65	40.05± 0.97	47.38± 0.93
	p=0.004	**p<0.001**	p=0.177	**p=0.021**	**p<0.001**
PRIOR SMOKERS†					
Quit time					
<6 months before interview (n=173)	6.75± 0.50	6.00± 0.45	62.39± 2.49	39.60± 1.34	49.22± 1.31
>6 months before interview (n=1077)	7.02± 0.42	6.15± 0.38	62.26± 2.14	40.48± 1.17	48.21± 1.11
	p=0.392	p=0.620	p=0.930	p=0.264	p=0.223
SMOKING AT THE TIME OF INTERVIEW					
Intention to quit smoking					
Yes (n=652)	7.70± 0.50	6.37± 0.43	59.04± 2.20	37.48± 1.30	45.22± 1.36
No (n=354)	7.18± 0.53	6.25± 0.46	61.08± 2.34	38.67± 1.38	46.38± 1.45
	p=0.064	p=0.629	p=0.120	p=0.073	p=0.126

Values are mean ± SE adjusted for age, gender, diagnostic category, education, diabetes, recurrent coronary heart disease, and history of stroke.; † Ever smoker, patients who have ever smoked but who where former smokers at the time of the recruiting diagnosis; prior smoker, patients who where smoking at the time of the recruiting diagnosis, but were former smokers at the time of the interview; smoker, patients still smoking at the time of interview; never smokers, patients who have never smoked.; EQ-VAS, EuroQoL visual analogue scale; HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS anxiety; HADS-D, HADS depression; MCS-12, SF-12 mental functioning; PCS-12, SF-12 physical functioning; SF-12, the 12-item short form health survey.

Table 3: Association between HRQoL and PHYSICAL ACTIVITY CHANGES

	HADS-A	HADS-D	EQ-VAS	PCS-12	MCS-12
COMPLETE SAMPLE					
Attempt to increase physical activity					
Yes (n=4967)	6.57± 0.22	5.56± 0.22	64.17± 1.33	39.90± 0.75	48.02± 0.66
No (n=3502)	7.14± 0.22	6.31± 0.22	60.69± 1.34	37.50± 0.75	46.82± 0.67
	p<0.001	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**
Physical activity level based on single question†					
No physical activity (n=1012)	7.62± 0.24	7.22± 0.24	55.53± 1.43	34.01± 0.84	44.93± 0.70
Light physical activity in most weeks (n=4999)	6.83± 0.22	5.90± 0.22	62.53± 1.34	38.81± 0.80	47.57± 0.64
Vigorous PA ≥20 min, ≤ 2x/week (n=1413)	6.20± 0.24	5.14± 0.24	67.21± 1.41	41.75± 0.83	48.71± 0.69
Vigorous PA ≥20 min, ≥3x/week (n=1197)	6.02± 0.24	4.90± 0.24	68.36± 1.43	42.44± 0.83	49.33± 0.70
	p<0.001	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**
IPAQ					
Low (n=1134)	7.21± 0.29	6.67± 0.29	57.21± 2.09	35.99± 1.02	46.20± 0.86
Moderate (n=1792)	6.24± 0.29	5.48± 0.29	63.65± 2.09	39.64± 1.02	49.31± 0.85
High (n=1679)	6.01± 0.30	5.09± 0.30	67.94± 2.10	41.03± 1.03	50.90± 0.87
	p<0.001	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**
Change in physical activity according to IPAQ classes					
Change in PA + low IPAQ (n=515)	7.02± 0.32	6.49± 0.31	58.55± 2.10	37.57± 1.03	46.56± 0.90
No change in PA + low IPAQ (n=591)	7.51± 0.32	6.95± 0.31	54.93± 2.09	33.90± 1.03	45.71± 0.90
Change in PA + moderate/high IPAQ (n=2093)	5.90± 0.30	5.09± 0.29	66.74± 2.01	40.83± 0.99	50.23± 0.84
No change in PA + moderate/high IPAQ (n=1264)	6.59± 0.30	5.66± 0.30	62.74± 2.04	38.82± 1.00	49.39± 0.86
	p<0.001	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**
PHYSICALLY INACTIVE PATIENTS‡					
Intention to become PA (if normal weight)					
Yes (n=200)	7.32± 0.49	5.80± 0.44	63.63± 2.43	41.12± 1.22	47.04± 1.25
No (n=736)	7.05± 0.42	6.30± 0.38	62.36± 2.14	37.87± 1.07	46.85± 1.07
	p=0.399	p=0.096	p=0.409	**p<0.001**	p=0.834
Intention to become PA (if overweight or obese)					
Yes (n=1098)	6.69± 0.29	6.00± 0.26	63.69± 1.47	39.10± 0.82	47.63± 0.79
No (n=3315)	7.01± 0.27	6.28± 0.25	60.29± 1.40	37.65± 0.79	46.64± 0.74
	p=0.025	**p=0.035**	**p<0.001**	**p<0.001**	**p=0.009**

Values are mean ± SE adjusted for age, gender, educational level, recruiting diagnosis, diabetes, history of stroke, and coronary recurring events.; † Which of the following four best describes your level of activity outside work?; ‡Physically inactive <3–5 times/week, 20–60 min/session.; EQ-VAS, EuroQoL visual analogue scale; HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS anxiety; HADS-D, HADS depression; IPAQ, International Physical Activity Questionnaire; MCS-12, SF-12 mental functioning; PCS-12, SF-12 physical functioning; SF-12, the 12-item short form health survey.

Table 4: Association between HRQoL and DIETARY CHANGES

	HADS-A	HADS-D	EQ-VAS	PCS-12	MCS-12
COMPLETE SAMPLE					
BMI at interview					
Normal (n=1572)	6.84± 0.23	5.92± 0.23	62.89± 1.38	39.45± 0.78	47.13± 0.69
Overweight (n=4055)	6.68± 0.22	5.72± 0.22	63.53± 1.34	39.59± 0.76	47.80± 0.66
Obese (n=3083)	6.90± 0.22	6.04± 0.22	61.89± 1.34	37.92± 0.76	47.39± 0.66
	p=0.052	**p=0.001**	**p=0.001**	**p<0.001**	P=0.056
Weight changes between recruiting diagnosis and interview					
≥5% weight loss (n=763)	6.78± 0.26	6.01± 0.25	62.87± 1.55	39.08± 0.84	46.91± 0.76
-5% <weight change <+5% (n=4066)	6.66± 0.23	5.77± 0.23	63.23± 1.45	39.46± 0.79	47.61± 0.69
≥5% weight gain (n=1496)	6.71± 0.25	5.95± 0.24	61.93± 1.50	38.56± 0.82	47.67± 0.73
	p=0.746	p=0.115	p=0.070	**p=0.012**	p=0.209
Attempt to eat healthier					
Change in fat intake					
Yes (n=7376)	6.77± 0.22	5.83± 0.22	62.94± 1.33	38.99± 0.76	47.57± 0.65
No (n=1285)	6.99± 0.24	6.24± 0.24	61.04± 1.42	37.95± 0.80	47.02± 0.70
	p=0.070	**p<0.001**	**p=0.001**	**p=0.001**	p=0.083
Reduction in salt intake					
Yes (n=6150)	6.77± 0.22	5.79± 0.22	63.19± 1.35	39.08± 0.76	47.58± 0.65
No (n=2417)	6.93± 0.23	6.08± 0.23	61.74± 1.39	38.44± 0.78	47.25± 0.68
	p=0.108	**p=0.001**	**p=0.002**	**p=0.010**	p=0.202
Increase in fish intake					
Yes (n=5818)	6.67± 0.22	5.73± 0.22	63.73± 1.35	39.12± 0.76	47.71± 0.65
No (n=2815)	7.08± 0.22	6.21± 0.23	60.90± 1.37	38.33± 0.77	47.09± 0.67
	p<0.001	**p<0.001**	**p<0.001**	**p=0.001**	**p=0.012**
Increase in fruit and vegetable intake					
Yes (n=6765)	6.73± 0.22	5.78± 0.22	63.18± 1.34	39.10± 0.76	47.55± 0.65
No (n=1886)	6.95± 0.23	6.19± 0.23	61.24± 1.39	38.32± 0.79	47.36± 0.68
	p=0.034	**p<0.001**	**p<0.001**	**p=0.003**	p=0.492
OVERWEIGHT AND OBESE PATIENTS					
Intention to lose weight					
Yes (n=3226)	6.90± 0.23	5.92± 0.22	62.21± 1.33	38.35± 0.79	47.66± 0.68
No (n=3524)	6.78± 0.23	5.91± 0.22	62.31± 1.33	39.16± 0.79	47.39± 0.68
	p=0.233	p=0.915	p=0.835	**p=0.001**	p=0.313

Values are mean ± SE adjusted for age, gender, educational level, recruiting diagnosis, diabetes, history of stroke, and coronary recurring events.; EQ-VAS, EuroQoL visual analogue scale; HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS anxiety; HADS-D, HADS depression; MCS-12, SF-12 mental functioning; PCS-12, SF-12 physical functioning; SF-12, the 12-item short form health survey.

These findings support the hypothesis of a vicious circle, where overweight and obese people who often experience difficulties in walking or climbing stairs, for example, are less inclined to become physically active, thus leading to an increase in weight, which again leads to less exercise (Bauman et al, 2012). Therefore, implementing multimodal interventions, focusing both on exercise, diet, and weight may be necessary. Lower HRQoL scores were found in smokers compared to non-smokers (both never smokers and former smokers). These results confirm the observations found in several studies conducted in the general population; however, for coronary patients, conflicting results have been found (Haddock et al, 2003; Piper et al, 2012; Quist-Paulsen et al, 2006; Schweikert et al, 2009; Taira et al, 2000). Even though patients who made an attempt to quit smoking had a higher HRQoL compared to those who did not, no significant difference could be found between attempters and non-attempters still smoking at interview, suggesting that only successful smoking cessation attempts will lead to a HRQoL increase. Furthermore, our results imply that HRQoL outcomes rapidly improve once patients stop smoking, because time since smoking cessation did not have an influence on HRQoL. Likewise, a study in the general population by Piper et al. showed that HRQoL improved quickly (1 year) after smoking cessation and that this improvement was sustained for at least 3 years (Piper et al, 2012). Within the Nurses' Health Study, HRQoL scores improved gradually with longer time since quitting (Sarna et al, 2008). In complete agreement with past research both in the general population as well as in coronary patients, our results have shown that, based on both subjective as well as standardized measures (IPAQ), low physical activity levels are associated with worse HRQoL scores (Bize et al, 2007; Sevinc et al, 2010). Conform the observations made by Martin et al. (Martin et al, 2009), our findings suggest that the improvements in HRQoL outcomes are associated with the amount of physical activity; however, the largest increase was seen between low and moderate IPAQ scores and a significant but lower effect was found between moderate and high IPAQ. Actions related with an increase in physical activity as well as the actual physical activity levels were associated with better HRQoL outcomes. These components seem to reinforce one another, with the highest HRQoL scores seen in patients residing in the highest IPAQ class, who had, moreover, made an attempt to increase their physical activity. In accordance with the literature, BMI was inversely associated with HRQoL (Oreopoulos et al, 2010; Schweikert et al, 2009). In contrast, regarding weight changes (≥5% weight loss; ± 5% weight change; ≥5% weight gain) between recruiting diagnosis and interview, no significant between-group differences were observed. In the general population, similar results were found, allowing us to conclude that the act of exercising and healthy eating behaviour themselves, and not merely losing weight, are aligned with a better HRQoL (Martin et al, 2009). Finally, dietary changes are associated with better HRQoL outcomes. Results from the SUN project have also found an important association between adherence to Mediterranean diet (consumption of fruit, vegetables, and fish and olive oil and reduction of meat and dairy intake) and better SF-36 scores (Henriquez Sánchez et al, 2012). Little is know about the clinical relevance of these differences in HRQoL, since no general consensus is available on what is perceived as a meaningful difference. Some authors have suggested half a standard deviation as the minimal important difference (MID) (Norman et al, 2003), while others have proposed a 3–5-point change for the SF-12 (Samsa et al, 1999), a MID of 0.074 for EQ-5D (Walters et al, 2005), and a MID of 1.5 for HADS (Puhan et al, 2008). When applying these rules, no clinical relevance could be found for most associations, with the exception of physical activity, with several items exceeding the MID. The limitations of our study have to be acknowledged in order to interpret the results correctly. Potential for recall bias exists, since most data were self-reported. Furthermore, there is potential confounding by social desirability bias. Patients may have overestimated their behavioural changes in order to present a more social acceptable image of themselves. Also, the included questions did not allow assessment of the degree to which an attempt was made to alter their behaviour. The questions included in the questionnaire were formulated as ‘steps taken to reduce your risk of CHD’. We have no information about when the patient has taken these steps, how many times, and whether or not the patient is still continuing with the action. Also, the cross-sectional study design does not allow assessment of the directionality of the association between HRQoL and lifestyle changes. However, the lack of association between the intention to accept a healthier lifestyle and patients’ HRQoL most likely indicates that the lifestyle changes induce better HRQoL outcomes and not the other way round. A longitudinal assessment as well as a more detailed questionnaire in order to gather further information on the ‘stage of change’ is needed in order to better understand the complex relationship between lifestyle changes and HRQoL. According to the transtheoretical model, behavioural changes can be divided in five different stages of change: the precontemplation stage, the contemplation stage, the preparation stage, the action stage and the maintenance stage (Prochaska et al, 1983; Romain et al, 2012). Furthermore, it is unclear whether these benefits in HRQoL are sustained over time or whether the gains are associated with a one-time benefit inherent to the change itself; hence, further research should focus on the long-term gains in HRQoL. In addition, patients included are not always representative for a country’s coronary patients, since data from selected geographical areas were used. The main strengths of our study are its large sample, including patients across Europe, and its ability to control for various confounders. Notwithstanding the limitations, out results reveal HRQoL gains associated with adopting a healthier lifestyle. The actual self-reported lifestyle changes – ceasing smoking, increasing physical activity, and adopting a healthy diet – and not the intention to change are associated with better HRQoL outcomes.

APPENDIX

Risk factor: Smoking		
Have you ever smoked?	☐ 1 Yes	☐ 2 No
Were you smoking in the month prior to the hospital admission for the index event or procedure?	☐ 1 Yes	☐ 2 No
Do you smoke now?	☐ 1 Yes	☐ 2 No
If not smoking now, did you quit within the last 6 months?	☐ 1 Yes	☐ 2 No
If not smoking now, did you quit more than 6 months ago?	☐ 1 Yes	☐ 2 No
If smoking now, are you seriously thinking of quitting smoking?	☐ 1 Yes, within the next 30 days ☐ 2 Yes, within the next 6 months ☐ 3 No, not thinking of quitting ☐ 4 Don't know/ Unsure	
Risk factor: Diet and Body Weight		
Are you seriously considering trying to lose weight to reach your goal in the next month?	☐ 1 Yes ☐ 2 No	☐ 3 Don't know/ Unsure
Are you seriously considering trying to lose weight to reach your goal in the next 6 months?	☐ 1 Yes ☐ 2 No	☐ 3 Don't know/ Unsure
Risk factor: Physical Activity		
Which of the following four best describes your level of activity outside work? *(Please continue getting to and from work, sporting activity and other physical effort during your leisure time, like gardening or dancing. Vigorous activity causes shortness of breath, a rapid heart rate, and sweating.)*	☐ 1 No physical activity weekly ☐ 2 Only light physical activity in most weeks ☐ 3 Vigorous physical activity at least 20 minutes once or twice a week ☐ 4 Vigorous physical activity for at least 20 minutes three or more times a week ☐ 5 Don't know/ Unsure	
Regular Exercise is any PLANNED physical activity (e.g., brisk walking, aerobics, jogging, bicycling, swimming, rowing, etc.) performed to increase physical fitness. *(Such activity should be performed 3 TO 5 TIMES per week for 20-60 MINUTES per session. Exercise does not have to be painful to be effective but should be done at a level that increases your breathing rate and causes you to break a sweat.)* Do you exercise regularly according to that definition?	☐ 1 Yes, I have been for MORE than 6 months ☐ 2 Yes, I have been for LESS than 6 months ☐ 3 No, but I intend to in the next 30 days ☐ 4 No, but I intend to in the next 6 months ☐ 5 No, and I do NOT intend to in the next 6 months ☐ 6 Don't know/ Unsure	

Which one of the following steps did you take SINCE THE INDEX EVENT OR PROCEDURE to reduce your risk of heart disease?			
Stop smoking			
Abstinence	☐ 1 Yes	☐ 2 No	☐ 3 Don't know/ Unsure
Reduction	☐ 1 Yes	☐ 2 No	☐ 3 Don't know/ Unsure
smoking cessation clinic	☐ 1 Yes	☐ 2 No	☐ 3 Don't know/ Unsure
nicotine replacement therapy	☐ 1 Yes	☐ 2 No	☐ 3 Don't know/ Unsure
Bupropion	☐ 1 Yes	☐ 2 No	☐ 3 Don't know/ Unsure
Other	☐ 1 Yes	☐ 2 No	☐ 3 Don't know/ Unsure
Healthy diet			
reduction of fat intake	☐ 1 Yes	☐ 2 No	☐ 3 Don't know/ Unsure
eating more fruits and vegetables	☐ 1 Yes	☐ 2 No	☐ 3 Don't know/ Unsure
eating more fish	☐ 1 Yes	☐ 2 No	☐ 3 Don't know/ Unsure
reducing sugar	☐ 1 Yes	☐ 2 No	☐ 3 Don't know/ Unsure
Increase physical activity			
following specific exercise advice from a health or exercise professional	☐ 1 Yes	☐ 2 No	☐ 3 Don't know/ Unsure
attending a fitness club or leisure centre	☐ 1 Yes	☐ 2 No	☐ 3 Don't know/ Unsure
trying to do more general everyday physical activities	☐ 1 Yes	☐ 2 No	☐ 3 Don't know/ Unsure
joining a community walking group	☐ 1 Yes	☐ 2 No	☐ 3 Don't know/ Unsure
Other	☐ 1 Yes	☐ 2 No	☐ 3 Don't know/ Unsure

Chapter 7. Association HRQoL/psychological distress and risk factor level awareness in coronary patients

Based on:

De Smedt D, Clays E, Annemans L, Pardaens S, Kotseva K, De Bacquer D, On behalf of the EUROASPIRE Study Group

Risk factor awareness in a coronary population is associated with better health-related quality of life outcomes.

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Abstract

Purpose: The purpose of this study was to investigate the risk factor level awareness in coronary patients and to assess its associations with health-related quality of life (HRQoL)/psychological distress.

Methods: Data from EUROASPIRE III (European Action on Secondary and Primary Prevention by Intervention to Reduce Events) was used. 8743 coronary patients from 22 European countries were interviewed and examined at least 6 months after their acute event. Patients were asked to complete EQ-5D, SF-12 and HADS instruments. Furthermore risk factor level awareness was assessed during interview.

Results: 81.7% of patients indicated to be aware of their own blood pressure level, whereas only 46.6% of patients indicated to be aware of their cholesterol level. Furthermore, 43.7% of patients were aware of their blood glucose level, whereas in diabetes patients blood glucose level awareness reached 81.8%. Risk factor level awareness was significantly associated with HRQoL/psychological distress, with patients being unaware of their risk factor levels having worse outcomes. The relationship between awareness and HRQoL/psychological distress seemed to be partly mediated by the attempt of patients to adopt a healthier behaviour, nevertheless, there was also a direct link between awareness and HRQoL/psychological distress.

Conclusion: Insufficient risk factor level awareness in coronary patients is associated with worse HRQoL/psychological distress, independent from patients' risk factor profile. Health care workers should be encouraged to inform their patients about the importance of their coronary risk factors, the actual level and their personal target.

1. Introduction

The major causes responsible for developing coronary heart disease (CHD) in addition to increasing age and genetic predisposition are elevated cholesterol level, high blood pressure, smoking, obesity, diabetes, physical inactivity and psychosocial stress (Perk et al, 2012). Therefore, in addition to optimized medical treatment, behavioural changes towards a healthier lifestyle are recommended. Smoking cessation, a healthy diet and an increase in physical activity are known to have a positive influence on CHD risk factors and consequently help to reduce the risk for a coronary event (Perk et al, 2012). Many coronary patients however, are unable to list the risk factors associated with CHD (Redfern et al, 2007). According to a study by Karthik et al. about half of coronary artery disease (CAD) patients identify smoking (53.6%) and high cholesterol (55.3%) as a risk factor. Blood pressure and family history were identified as a risk factor by only two in five patients (43% and 42.5% respectively) and no more than 14.5% and 13.6% of patients know that diabetes and obesity are risk factors for CHD (Karthik et al, 2006). Furthermore, they observed that only one in two patients taking CHD medication have knowledge about its role in their treatment (Karthik et al, 2006). Moreover, few CHD patients are aware about their own risk factor profile. Cheng et al. found that two thirds of CAD patients were aware of their own blood pressure level and only 45.3% of patients reported to be aware of their cholesterol level (Cheng et al, 2005b; Cheng et al, 2005a). Similar results were found in the general population, with only 51% of US citizens being aware of their own cholesterol level (Nash et al, 2003).

This lack of patient awareness could result in low adherence to lifestyle changes and prescribed medication. A better knowledge and understanding of CHD risk factors as well as patients' knowledge about their own coronary heart disease risk factors correlates with improved patient behaviour, both concerning self-reported lifestyle changes as well as medication adherence, which can lead to better cardiovascular outcomes (increase in survival, decrease in cardiac events) (Alm-Roijer et al, 2004, Alm-Roijer et al, 2006). According to Grover et al (2007) discussing the coronary risk profile with the patient is associated with a small but measurable improvement in the efficacy of lipid therapy (Grover 2007). Recently however, in addition to the more objective clinical measures, many patients consider the health-related quality of life (HRQoL) equally important. HRQoL is a multidimensional concept assessing the effect of a disease, its treatment and symptoms on patients' physical, emotional and social well-being. Prior studies have found an association between impaired HRQoL, anxiety, depression and worse long-term cardiovascular outcomes (Kurdyak et al, 2011; Spertus et al, 2002; Thombs et al, 2008).

The purpose of the current study is twofold. Firstly, we wanted to investigate the risk factor awareness in a large European sample of coronary patients. Secondly, we hypothesized that risk factor awareness in CHD patients will be associated with an improved HRQoL and with less psychological distress. Furthermore, we wanted to examine whether such an association is mediated by lifestyle changes or yet another mechanism. This issue has not yet been addressed previously.

2. Methods

Data collection

Data were extracted from the EURopean Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE III) study, a cross-sectional survey performed in 2006-2007 across 22 European countries: Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, Romania, Russian Federation, Slovenia, Spain, The Netherlands, Turkey, and the United Kingdom (UK). More details on this survey can be found elsewhere (Kotseva et al, 2009b). Briefly, patients aged between 18 and 80 years, hospitalized for coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), acute myocardial infarction (AMI) or myocardial ischemia, were retrospectively identified from diagnostic registers, hospital discharge lists or other sources.

Patients were invited for interview and physical examination. Data collection was organized in a standardized way by trained research staff. In total, 8,966 patients (participation rate=73%) were interviewed and examined at least 6 months and not later than 3 years after their initial hospital admission (median=1.24 years).

The following information was obtained: personal and demographic details, medical and in particular cardiovascular history, family history of CHD, reported lifestyle, lifestyle changes and risk factor management related to exercise, diet, smoking and medical treatment. Patients were also asked "*Whose care are you currently (in the last three months) under for your cardiac condition*". Weight, height, waist circumference, blood pressure (BP), heart rate, breath carbon monoxide, serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides, low-density lipoprotein cholesterol (LDL-C), blood glucose and glycated haemoglobin (HbA1c) in patients with diabetes, were measured. The risk factor targets used, were based on the European guidelines on cardiovascular prevention (Perk et al, 2012). Raised BP was defined as systolic blood pressure (SBP)/ diastolic blood pressure (DBP) ≥140/90 mm Hg (≥130/80 mm Hg in patients with diabetes). Raised TC was defined as TC ≥4.5 mmol/L. Raised blood glucose was defined as blood glucose ≥6.1 mmol/L. Low physical activity was defined as less than 20 min moderate physical activity, three times a week. Central obesity was defined as waist circumference >102/88 cm (men/women).

In addition, patients were asked to complete 3 validated self-administered measures to assess their HRQoL and psychological distress: the EuroQoL-5D (EQ-5D), the 12-item short form health survey (SF-12), and the Hospital Anxiety and Depression Scale (HADS) (De Smedt et al, 2013b). The EQ-5D is a commonly used, easy to complete, standardized instrument to measure health status, containing a descriptive part (EQ_{index}) and a visual analogue scale (EQ-VAS). The former covers 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with three response categories each (no problems, some problems, or severe problems). The answers on these dimensions provide a simple descriptive profile from which an index score can be calculated, with 1 representing perfect health, 0 representing death, and <0 representing a health state perceived worse than death. The EQ-VAS a 20 cm vertical scale on which the patient is asked to indicate how good or bad their current health status is from 0 (worst imaginable) to 100 (best imaginable) (Rabin et al, 2011). The SF-12 (second version) emerges from the SF-36, but includes only 12 Likert scale questions, covering eight dimensions: general health, physical functioning, role physical, bodily pain, vitality, social functioning, role emotional, and mental health. Both a physical (PCS-12) and mental functioning (MCS-12) component score, ranging between 0 and 100, can be calculated using a norm-based scoring algorithm. Lower scores represent worse and higher scores represent better self-perceived HRQoL outcomes (Ware et al, 2002). The SF-12 was not administered in Hungary. The HADS instrument finally, merely covers psychological issues, and it is useful in assessing the mental health status of patients. It contains seven items related to anxiety and seven related to depression, each with a 4-point response scale. Item scores can be added to obtain the summary scores on anxiety (HADS-A) and depression (HADS-D) separately. The total score on each subscale ranges between 0 and 21 with higher scores representing worse outcomes (Zigmond et al, 1983).

Furthermore, risk factor level awareness were assessed during interview. Patients were asked the following questions: "*Are you aware of your latest blood pressure/ total cholesterol/ blood glucose level? YES/NO*"

Statistical analyses

Risk factor level awareness variables were investigated both as separate items and as a combination of variables. The combined variable incorporated BP, TC and blood glucose level awareness. Hence patients could be aware on 0, 1, 2 or 3 risk factor levels. The first was labelled as unaware whereas the latter three were categorized as aware of at least one risk factor. Descriptive analyses were performed in order to gain knowledge about gender and country specific risk factor level awareness rates. Chi² tests and the Kruskal-Wallis tests were used to assess characteristics associated with awareness. Furthermore, a multilevel linear model, with HRQoL as continuous outcomes was used in order to account for the clustering of patients within countries (random effect). No interaction with gender was seen, hence instead of performing the analyses separately for males and females, gender was included as covariate in the analyses. Initial adjustment for age, gender, education and country was carried out and further adjustment for lifestyle changes was applied (fixed effect). Analyses were performed using IBM SPSS version 21. Significance levels were set at $p < 0.05$.

3. Results

Of the 8966 eligible patients, 8743 patients provided valid HRQoL and awareness information. Their mean age was 63.2 years (SD=9.5), 74.6% were male, and 25.3% had only received a low education. At the time of the interview 24.5% had diabetes, 35.4% was obese and 49.0% was central obese, 16.9% were smoking, 69.7% reported a low physical activity level, 51.3% had a raised TC and 56.1% had a raised BP, 79.7% and 70.5% were taking lipid lowering and antihypertensive medication respectively.

According to the patients, risk factors measurement since index hospitalization was not always done: 96.6% of patients have indicated that their BP was measured, 87.4% of patients stated that their TC was measured and 80.1% and 94.4% of the complete sample and the diabetes patients respectively, reported that their blood glucose was measured since their index hospitalization.

Risk factor level awareness among patients was highest with regard to BP, with 81.7% of patients indicating to be aware of their own level. With regard to cholesterol only 46.6% of patients indicated to be aware of their own TC level. Furthermore, 43.7% of the complete sample was aware of their blood glucose level, whereas in diabetes patients blood glucose level awareness reached 81.8% (Table 1).

Table 1: Risk factor level awareness in coronary patients, stratified by age and gender

	ALL , % aware(n)	MALE , % aware(n)			FEMALE , % aware(n)		
		≤65 year	>65 year	p-value*	≤65 year	>65 year	p-value*
TC level	46.6(4076/8743)	48.0(1826/3803)	44.8(1217/2719)	0.009	49.9(471/943)	44.0(562/1278)	0.005
BP level	81.7(7143/8743)	80.7(3069/3803)	83.0(2257/2719)	0.019	81.8(771/943)	81.8(1046/1278)	0.989
BG level	43.7(3824/8743)	**40.3(1532/3803)**	**45.2(1229/2719)**	<0.001	**46.9(442/943)**	**48.6(621/1278)**	0.433
BG level (if diabetes)	81.8(1734/2120)	82.9(655/790)	**82.3(552/671)**	0.745	84.6(225/266)	**76.8(302/393)**	0.015

TC: total cholesterol; BP: blood pressure; BG: blood glucose
* Significance between age groups
In bold: significant difference between gender, categorized by age

No consistent distinction in awareness rates could be observed across age groups. Furthermore, in those patients aged 65 years or younger, risk level awareness did not differ substantially between males and females, except for blood glucose. In those patients above 65 years, females were more likely to be aware of their blood glucose level, except in diabetes patients were males were more aware about their level (table 1).

Furthermore, a great variation in awareness can be seen across countries (table 2). The lowest patient awareness was seen in Ireland and the UK with the proportion of patients being aware on at least one out of three risk factor levels amounting to 61.3% and 63.4% respectively. Only 2.9% of Irish and 8.1% of UK patients were perfectly aware on all three risk factors. In contrast, more than half of the Russian (62.8%), Greek (56.7%) and Cypriot (52.3%) patients were fully aware on all three risk factors.

Additionally, a within country variation is observed with great awareness on some risk factors and very low awareness on others. In Belgium for example, a high proportion of patients was aware of his/her own blood pressure level (87.1%), whereas a minority of patients were aware of their blood glucose level (18.9%). Similarly, the blood pressure awareness in Spanish patients (84.2%) is high whereas less than 1 in 4 patients is aware on their total cholesterol level (23.6%). Likewise, although the awareness on blood pressure and blood glucose in Irish (23.1% and 15.3% resp.) and UK patients (34.8% and 22.0% resp.) is very low the proportion of patients being aware on their total cholesterol level is rather average (47.8% and 46.3%).

Table 2: Risk factor level awareness in coronary patients across Europe

COUNTRY	TC-level, % aware(n)	BP-level, % aware(n)	BG-level, % aware(n)	Perfectly aware, % aware(n)
Belgium	39.6 (111/280)	87.1 (244/280)	18.9 (53/280)	8.9 (25/280)
Bulgaria	25.1 (135/538)	78.4 (422/538)	33.3 (179/538)	15.8 (85/538)
Croatia	35.1 (158/450)	84.4 (380/450)	43.8 (197/450)	23.1 (104/450)
Cyprus	59.9 (260/434)	86.4 (375/434)	66.6 (289/434)	52.3 (227/434)
Czech Republic	48.0 (228/475)	87.4 (415/475)	45.3 (215/475)	30.7 (146/475)
Finland	60.3 (143/237)	75.5 (179/237)	41.8 (99/237)	30.8 (73/237)
France	56.4 (171/303)	94.7 (287/303)	54.5 (165/303)	40.9 (124/303)
Germany	38.5 (212/550)	80.4 (442/550)	31.5 (173/550)	16.0 (88/550)
Greece	78.3 (94/120)	74.2 (89/120)	64.2 (77/120)	56.7 (68/120)
Hungary	42.5 (194/457)	91.5 (418/457)	63.5 (290/457)	33.5 (153/457)
Ireland	47.8 (184/385)	23.1 (89/385)	15.3 (59/385)	2.9(11/385)
Italy	50.9 (192/377)	97.1 (366/377)	49.9 (188/377)	34.7 (131/377)
Latvia	57.6 (299/519)	91.1 (473/519)	47.8 (248/519)	39.3 (204/519)
Lithuania	53.7 (273/508)	95.7 (486/508)	38.8 (197/508)	25.6 (130/508)
Poland	48.8 (245/502)	92.0 (462/502)	52.6 (264/521)	36.1 (181/502)
Romania	53.0 (276/521)	91.2 (475/521)	49.5 (258/521)	39.7 (207/521)
Russian Federation	66.7 (273/409)	94.4 (386/409)	68.0 (278/409)	62.8 (257/409)
Slovenia	57.0 (167/293)	93.5 (274/293)	57.3 (168/293)	41.0 (120/293)
Spain	23.6 (119/505)	84.2 (425/505)	37.8 (191/505)	11.1 (56/505)
The Netherlands	47.1 (105/223)	66.8 (149/223)	22.0 (49/223)	11.2 (25/223)
Turkey	26.3 (88/335)	58.2 (195/335)	34.6 (116/335)	16.7 (56/335)
United Kingdom	46.3 (149/322)	34.8 (112/322)	22.0 (71/322)	8.1 (26/322)
Male	46.7 (3043/6523)	81.6 (5326/6523)	42.3 (2761/6523)	27.9 (1820/6523)
Female	46.5 (1033/2222)	81.8 (1817/2222)	47.8 (1063/2222)	30.5 (677/2222)
≤65 years	48.4 (2297/4746)	80.9 (3840/4746)	41.6 (1974/4746)	28.0 (133/4746)
>65 years	44.5 (1779/3999)	82.6 (3303/3999)	46.3 (1850/3999)	29.2 (1167/3999)

TC: total cholesterol; BP: blood pressure; BG: fasting glucose; Perfectly aware= aware on TC, BP and FG level

Information on the patient characteristics in relation to their awareness can be found in table 3. A greater proportion of revascularization (PCI and CABG) is seen in those patients more aware. Patients with diabetes, obesity, a raised TC or raised BP were more aware of their own levels. Similarly, patients taking antihypertensive medication or lipid lowering medication were more aware of their own levels. Patients not aware of their own levels were more likely to be lower educated, to be smokers and to be low physically active.

Multilevel analyses revealed a significant association between awareness and HRQoL (table 4). Patients not aware of their own risk factor levels reported lower HRQoL outcomes compared to those being partially or fully aware. Especially the mental components seem to be significantly associated with awareness, whereas no gradual effect was seen on the physical component (PCS-12). Analyses on the individual HRQoL dimensions produced similar results with better HRQoL outcomes in those more aware.

Table 3: Characteristics of awareness

	Unaware n=1081	Aware on 1 risk factor level n=2778	Aware on 2 risk factor levels n=2387	Aware on 3 risk factor levels n=2497	
Male, %(n)	73.9(799/1081)	76.9 (2136/2778)	74.0 (1767/2387)	72.9 (1820/2497)	P=0.007
Age, mean (SD)	63.1(10.6)	62.9 (9.7)	63.3 (9.0)	63.5 (9.2)	P=0.406
Recruiting diagnosis: revascularization, %(n)	54.8(592/1081)	59.1 (1642/2778)	63.4 (1514/2387)	62.7 (1566/2497)	P<0.001
Low education, %(n)	35.8(385/1074)	28.2 (778/2759)	23.9 (567/2374)	18.8 (469/2490)	P<0.001
Diabetes, %(n)	12.1(129/1069)	12.4 (342/2750)	35.8 (850/2376)	32.3 (799/2472)	P<0.001
Blood glucose, mean (SD)	6.6 (2.0)	6.69 (1.78)	7.41 (2.66)	7.23 (2.37)	P<0.001
BMI, mean (SD)	28.6(4.6)	28.7 (4.4)	29.2 (4.5)	28.9 (4.4)	P=0.003
Obese, %(n)	32.6(351/1077)	34.4 (952/2766)	37.3 (886/2375)	35.9 (894/2490)	P=0.030
Central obesity, %(n)	45.2(483/1068)	47.5 (1300/2738)	53.1 (1255/2364)	48.3 (1189/2464)	P<0.001
Low physical activity level, %(n)	75.5(793/1051)	68.6 (1882/2742)	67.3 (1585/2355)	70.8 (1750/2472)	P<0.001
TC, mean (SD)	4.6(1.3)	4.7 (1.2)	4.7 (1.2)	4.7 (1.2)	P=0.097
Raised TC, %(n)	47.9(487/1016)	52.1 (1369/2627)	50.6 (1132/2239)	52.7 (1260/2393)	P=0.056
Lipid lowering medication, %(n)	75.4(807/1071)	75.7 (2089/2761)	81.0 (1925/2377)	84.8 (2115/2493)	P<0.001
SBP, mean (SD)	138.3(21.0)	140.5 (21.4)	141.7 (20.7)	139.6 (19.6)	P<0.001
DBP, mean (SD)	81.7(12.0)	82.9 (12.2)	83.1 (11.7)	82.7 (11.0)	P=0.004
Raised BP, %(n)	50.0(539/1079)	53.3 (1478/2773)	60.6 (1445/2383)	57.5 (1434/2492)	P<0.001
Antihypertensive medication, %(n)	57.1(609/1067)	71.4 (1976/2768)	72.7 (1731/2382)	73.2 (1821/2489)	P<0.001
Smoking, %(n)	24.9(268/1078)	20.1 (555/2766)	13.9 (332/2384)	12.9 (323/2496)	P<0.001
Cardiac rehabilitation, %(n)	59.9(276/461)	73.1 (934/1277)	81.3 (943/1158)	80.9(792/979)	P<0.001
Under cardiologist care, %(n)	61.4(662/1079)	67.9(1883/2773)	69.5(1657/2385)	76.9(1919/2494)	P<0.001
Under GP care, %(n)	54.9(592/1079)	54.3(1507/2773)	54.5(1299/2385)	48.5(1209/2494)	P<0.001
Under no care, %(n)	5.4(58/1079)	2.7(76/2773)	2.3(55/2385)	1.3(33/2494)	P<0.001

RD: recruiting diagnosis; TC: total cholesterol; BP: blood pressure; GP: general practitioner

Table 4: Association awareness and HRQoL/psychological distress

	MCS-12		PCS-12		EQVAS		HADSA		HADSD	
	Mean (SE)	p-value	Mean (SE)	p-value	Mean (SE)	p-value	Mean (SE)	p-value	Mean (SE)	p-value
Unaware	47.74(0.69)[a]	REF[c]	41.37(0.80)	REF	64.92(1.42)	REF	6.26(0.21)	REF	5.76(0.24)	REF
1 aware	48.29(0.62)	0.186	42.35(0.74)	0.014	66.98(1.30)	0.006	5.82(0.21)	0.001	5.28(0.22)	0.001
2 aware	48.92(0.63)	0.006	41.95(0.74)	0.156	66.46(1.31)	0.045	5.79(0.21)	0.001	5.01(0.22)	<0.001
3 aware	49.27(0.63)	0.001	42.00(0.74)	0.133	67.25(1.31)	0.003	5.74(0.24)	0.001	4.91(0.22)	<0.001
	P<0.001[b]		**P=0.083**		**P=0.019**		**P=0.004**		**P<0.001**	

[a] Adjusted means
[b] P-values adjusted for age, gender, education, country
[c] Post hoc paired comparison

More detailed analyses of individual awareness variables revealed a significant association between HRQoL/psychological distress and TC level awareness both in patients with an elevated TC (≥4.5mmol/L) as well as in patients on cholesterol target (<4.5mmol/L), with better outcomes in patients who are aware about their cholesterol level. Likewise a significant association was found between HRQoL/psychological distress and BP level awareness, with the exception of MCS-12, PCS-12 and HADS-A in patients with an elevated BP. Blood glucose awareness did not seem to be associated with HRQoL/psychological distress, neither in those on target or above target. In diabetes patients however a significant association between blood glucose awareness and the EQ-5D index, MCS-12, HADS-D was found (table 5). Additional analyses for lifestyle changes resulted in a reduction of the mean effect size; however significant associations remained mostly significant except for the EQ-VAS.

Table 5: association between HRQoL/psychological distress and risk factor level awareness stratified by risk profile (mean (SE))

	% (N)	EQ-VAS	MCS-12	PCS-12	HADSA	HADSD
Complete sample						
TC < 4.5						
Not aware TC level	54.3(2187/4028)	66.292(1.325)[a]	48.227(0.576)	42.738(0.699)	5.906(0.219)	4.714(0.207)
Aware TC level	45.7(1841/4028)	68.204(1.328)	49.608(0.578)	41.552(0.698)	6.375(0.218)	5.335(0.206)
		P=0.002[b]	P<0.001	P<0.001	P<0.001	P<0.001
		p=0.357[c]	p=0.032	p=0.039	P=0.029	P=0.006
TC ≥ 4.5						
Not aware TC level	52.4(2228/4249)	65.339(1.351)	47.718(0.699)	41.576(0.773)	6.557(0.220)	5.568(0.219)
Aware TC level	47.6(2021/4249)	66.882(1.351)	48.978(0.698)	42.158(0.773)	6.310(0.220)	5.018(0.219)
		P=0.008	P<0.001	P=0.058	P=0.043	P<0.001
		P=0.130	P<0.001	P=0.214	P=0.028	P=0.003
BP <140/90 (130/80)						
Not aware BP level	20.1(769/3832)	65.527(1.521)	47.547(0.709)	41.712(0.827)	6.744(0.269)	5.720(0.265)
Aware BP level	79.9(3063/3832)	67.880(1.381)	48.974(0.616)	42.536(0.755)	6.099(0.233)	4.835(0.235)
		P=0.005	P=0.002	P=0.065	P<0.001	P<0.001
		P=0.193	P=0.044	P=0.255	P=0.014	P=0.003
BP ≥140/90 (130/80)						
Not aware BP level	16.9(830/4897)	64.294(1.431)	48.102(0.737)	41.148(0.811)	6.467(0.246)	5.668(0.253)
Aware BP level	83.1(4067/4897)	66.112(1.287)	48.806(0.651)	41.744(0.741)	6.251(0.210)	5.190(0.223)
		P=0.021	P=0.109	P=0.155	P=0.181	P=0.002
		P=0.309	P=0.789	P=0.789	P=0.296	P=0.267
BG <6.1mmol/L						
Not aware FG level	67.1(1380/2057)	67.723(1.464)	48.382(0.672)	43.065(0.857)	6.355(0.282)	5.111(0.235)
Aware FG level	32.9(677/2057)	67.343(1.542)	48.964(0.727)	41.989(0.896)	6.356(0.301)	4.912(0.255)
		P=0.668	P=0.249	P=0.024	P=0.995	P=0.265
		P=0.511	P=0.574	P=0.029	P=0.766	P=0.851
BG ≥6.1mmol/L						
Not aware FG level	50.2(2224/4434)	66.263(1.302)	48.05(0.642)	42.197(0.715)	6.198(0.222)	5.372(0.222)
Aware FG level	49.8(2210/4434)	65.554(1.305)	48.545(0.644)	41.408(0.717)	6.342(0.222)	5.313(0.223)
		P=0.587	P=0.126	P=0.008	P=0.228	P=0.592
		P=0.190	P=0.519	P=0.012	P=0.286	P=0.199
If diabetes						
BG <6.1mmol/L						
Not aware FG level	22.5(29/129)	60.268(4.335)	44.241(2.303)	42.034(2.520)	6.601(0.822)	6.998(0.742)
Aware FG level	77.5(100/129)	64.714(2.694)	46.810(1.361)	39.760(1.823)	6.326(0.501)	5.330(0.417)
		P=0.293	P=0.276	P=0.297	P=0.743	P=0.037
		P=0.584	P=0.468	P=0.158	P=0.642	P=0.154
BG ≥6.1mmol/L						
Not aware FG level	17.6(241/1367)	61.507(1.863)	44.840(0.918)	39.082(1.055)	6.885(0.325)	6.584(0.309)
Aware FG level	82.4(1126/1367)	62.658(1.480)	47.728(0.662)	39.475(0.881)	6.473(0.226)	5.739(0.215)
		P=0.411	P=0.000	P=0.584	P=0.153	P=0.002
		P=0.104	P=0.000	P=0.370	P=0.047	P=0.005

TC: total cholesterol; BP: blood pressure; BG: Blood glucose
[a] Adjusted means (for age, gender, education and country)
[b] p-values adjusted for age, gender, education and country
[c] p-values adjusted for age, gender, education, attempt to increase physical activity, attempt to quit smoking, attempt to eat healthier and country

4. Discussion

The importance of lifestyle changes and medication compliance is well-known in cardiovascular prevention (Perk et al, 2012; Rasmussen et al, 2007). In order to change behaviour, knowledge of CHD risk factors is essential (Nash et al, 2003) and improved illness understanding and risk factor awareness have been shown to correlate with increased compliance to lifestyle changes and medication intake (Alm-Roijer et al, 2004; Alm-Roijer et al, 2006; Baroletti et al, 2010; Grover et al, 2007). Patients who are involved in their medical care report less discomfort, greater alleviation of symptoms, more improvement in their general medical condition, less concern with their illnesses, a greater sense of control of their illnesses, and more satisfaction with their physicians (Brody et al, 1989). Hence patients should be empowered to take charge of their own health, also known as 'patient empowerment'. Empowerment in patients with long term conditions has been defined as: "a*n enabling process or outcome arising from communication with the health care professional and a mutual sharing of resources over information relating to illness, which enhances the patient's feelings of control, self-efficacy, coping abilities and ability to achieve change over their condition"*(Small et al, 2013). Four milestones can be considered in the evolution to patient empowerment. The first step is to make patients aware of their condition and to inform them. There is a change from passive to active participation in the disease treatment. When the patient is aware about his/her own health status, proper action plans and guidance can result in better adherence to treatment plans and consequently better health outcomes (Calvillo et al ,2013).

Our study results have shown insufficient risk factor level awareness among coronary patients, especially with regard to their own TC and blood glucose level and target. Those patients not aware about any of their risk factor levels, were more likely to have a lower education, to be low physically active or to be a smoker, whereas those aware on some or all of their own risk factor levels were more likely to have diabetes, to be obese, to have a raised TC, to have a raised BP or to have a high blood glucose. Hence, according to our results, patients with increased risk factor levels are more likely to be aware of their TC, BP or blood glucose level.

Furthermore, risk factor level awareness was associated with HRQoL and psychological distress, independent from patients' risk factor profile. In patients on target as well as in patients above target, awareness was associated with better outcomes. The relationship between awareness and HRQoL seems to be partly mediated by the attempt of patients to adopt a healthier behaviour. Patients with a greater awareness are more likely to have made attempts in order to improve their lifestyle. And lifestyle improvements have been shown to improve patients' HRQoL/psychological distress outcomes (De Smedt et al, 2013a; Ludt et al, 2011). Nevertheless, there also seems to be a direct association between awareness and HRQoL, particularly with the mental component. Patients more aware, report less anxiety and depression and score better on their mental and emotional well-being regardless of whether they change their lifestyle behaviour. Due to the cross-sectional design of the EUROASPIRE III survey, the causality of this association could not be explored. Awareness of their own risk factor levels might result in less mental distress and a better self-perceived health status. One possible explanation for this hypothesis, might be that patient involvement in their care and awareness of their risk factor profile could possibly affect their illness perception and sense of control. Poor illness perception and low sense of control have been associated with worse physical and mental HRQoL (Lau-Walker et al, 2009; Stafford et al, 2009). Hence, in addition to improved adherence to lifestyle changes, a better sense of control might also lead to a decrease in anxiety (French et al, 2005). However, there could just as well exist a reverse causality, with better HRQoL/psychological distress ensuring a greater interest of patients in their own risk factor profile. Most likely, some interplay exists between the above described pathways reinforcing one another.

Within our knowledge this is the first study to assess the association between awareness and HRQoL/psychological distress in coronary patients. Some studies have already investigated risk factor awareness in the general population, however various definitions of awareness have been used making comparison difficult. In the general population, where hypertensive patients who were aware of their elevated BP had worse HRQoL outcomes, compared to those persons unaware of their hypertension (Korhonen et al, 2011; Mena-Martin et al, 2003). This result can be largely attributed to the labelling effect, which can induce anxiety and depression because of the awareness of the elevated coronary and mortality risks associated with hypertension (Mena-Martin et al, 2003). Likewise, a higher sick leave is reported in persons aware of their hypertension status (Leynen et al, 2006). In the current analyses however, there was no labelling effect, since all patients included in EUROASPIRE III were already aware of their coronary condition.

Although the EUROAPSIRE survey is a unique database with information collected in a standardized way from a large sample of coronary patients across 22 European countries, our study also has some noteworthy limitations. First of all, as already mentioned, it is not possible to assess causality due to the study design, hence longitudinal studies are needed in order to draw conclusions about the directionality between risk factor level awareness and HRQoL/psychological distress. Secondly, those patients participating in the study are most likely those patients interested in their own health. Whether or not patients are interested in their own health is likely to be a determinant in the awareness of risk factor levels and targets. Therefore the above reported insufficient risk factor level awareness rates might be an underestimation. We were not able to adjust for the time since last measurement, hence this could potentially have had an influence on the result. Adjusting for the time since hospitalization however, did not alter the results significantly. In addition, it could be questioned whether awareness was measured in the best possible way. The question was translated in different languages, potentially resulting in small differences causing variation in interpretation across different patients. Further research should focus on how awareness can be assessed adequately. Furthermore, we were not able to adjust for income or socio-economic status, since these variables were not collected. Likewise, the organisation of the health care system in a given country, will have a substantial influence on the risk factor level awareness rates. Finally, it should be mentioned that patients are not a representative sample of all patients with CHD in each country, since they were identified from selected geographical areas and cardiac centres, hence caution is required when generalizing these results.

In conclusions, risk factor awareness among coronary patients is still suboptimal. An important finding, since this has been shown to be associated with worse compliance with medication and lifestyle changes. Furthermore risk factor level awareness seems to be associated with improved HRQoL and psychological distress. Future research should aim to investigate the directionality of this association using longitudinal follow up studies. Are patients with a better health status and less emotional distress, more interested in their risk factor profile. Or does knowledge about their own risk factor profile result in improved HRQoL outcomes.

Chapter 8.
Interchangeability between EQ-5D and SF-12

Based on:

De Smedt D, Clays E, Annemans L, De Bacquer D.

EQ-5D versus SF-12 in coronary patients. Are they interchangeable?

Value in Health. In press

Abstract

Objectives: The aim of the current study was to compare EQ-5D and SF-6D (based on SF-12) utility scores using a large European sample of stable coronary heart disease (CHD) patients. Special attention was given to country-specific results.

Methods: Data from the EUROASPIRE III (EURopean Action on Secondary and Primary Prevention by Intervention to Reduce Events) survey were used. Patients hospitalized for a coronary artery bypass graft, percutaneous coronary intervention, acute myocardial infarction or myocardial ischemia were interviewed and examined at least 6 months after their acute event. Health-related quality of life (HRQoL) was assessed using the EQ-5D and the SF-12. SF-12 outcomes were converted to SF-6D utility values, allowing comparison between both measures.

Results: Both EQ-5D and SF-6D results were available for 7,472 CHD patients from 20 European countries. The measures were significantly correlated (ICC=0.536), however, large differences between the two measures remain. 28.8% of patients reported a ceiling effect on the EQ-5D instrument, whereas only 4.2% of patients reported full health based on the SF-6D. Especially the mental component does not seem to be completely captured by the EQ-5D instrument. Furthermore, patients with worse EQ-5D outcomes were more likely to have better SF-6D results, whereas patients with better EQ-5D outcomes were more likely to have worse SF-6D results.

Conclusions: Both measures are not interchangeable. Whereas the main disadvantage of the EQ-5D is its ceiling effect, the potential advantages of SF-12 might disappear when converting the outcomes into an SF-6D utility, due to the small differences between patients.

1. Introduction

Patients' self-reported health-related Quality of Life (HRQoL) is increasingly considered an important outcome of medical treatment, especially in chronic conditions, such as coronary heart disease (CHD), where patients are being monitored for a considerable period of time. CHD is often a cause of pain, increased anxiety, and functional and social limitations, hence coronary patients are likely to have an impaired HRQoL (Mols et al, 2009; Thombs et al, 2006; Xie et al, 2008). Many different disease-specific as well as general measures exist to assess HRQoL in CHD patients such as: the MacNew Heart Disease Health-related Quality of Life Questionnaire (MacNew); the Seattle Angina Questionnaire (SAQ); the Myocardial Infarction Dimensional Assessment Scale (MIDAS); the 36-Item Short Form Health Survey (SF-36); the 12-Item Short Form Health Survey (SF-12); the Health Utility Index (HUI); the EuroQol-5D (EQ-5D); etc. However, few of these HRQoL measures generate a single preference based utility measure of health. Utilities are particularly useful in the calculation of cost-effectiveness ratio's (ICER), for computing health benefits expressed in quality adjusted life years (QALYs). The results of such evaluations enable decision makers to set priorities with regard to the reimbursement of health care, hence the validity of utilities is of great importance. EQ-5D is the most commonly used instrument to calculate utilities for cost-effectiveness analysis purposes. However, an algorithm developed by Brazier et al. in 2004 made it possible to calculate a utility score based on SF-12 by converting the measure in a 6-dimensional health state classification (SF-6D) (Brazier et al, 2004b; Kharroubi et al, 2007; McCabe et al, 2006). Some concern exists regarding the comparability between the utility score calculated from EQ-5D and the one based on SF-12 (Bharmal et al, 2006; Brazier et al, 2004a; Bryan et al, 2005; Ferreira et al, 2008). A recent study by Joore et al. (2010) reported remarkable differences in cost-effectiveness results, depending on the instrument used. Patients with mild health conditions had higher EQ-5D scores, whereas patients with severe conditions had higher SF-6D scores (Joore et al, 2010). This leads to better or worse cost-effectiveness outcomes, depending on the HRQoL instrument used. The incomparability of the results using different instruments poses a real threat on the usefulness and credibility of cost-effectiveness analyses .

Existing literature regarding the comparison of the EQ-5D and SF-6D in coronary patients is scarce. Only one study reported on this comparison, however the SF-6D scores were based on SF-36 outcomes and the sample size was relatively small (n=561) (van Stel et al, 2006). They concluded that in coronary patients EQ-5D and SF-6D are quite different from each other. The aim of the current study was to compare the EQ-5D and the SF-6D (based on SF-12) utility scores using a large European sample of coronary patients, with an additional focus on country-specific results.

2. Methods

Coronary Sample

Analyses were based on EUROASPIRE III (EURopean Action on Secondary and Primary Prevention by Intervention to Reduce Events) data, a cross-sectional survey performed in 2006-2007 across Europe. More details on this survey can be found elsewhere (Kotseva et al, 2009b). Briefly, patients aged between 18 and 80 years, hospitalized for coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), acute myocardial infarction (AMI) or myocardial ischemia, were retrospectively identified from diagnostic registers, hospital discharge lists or other sources. In total, 8966 patients (participation rate=73%) were interviewed and examined at least 6 months and not later than 3 years after their initial hospital admission (median time=1.24 years). During interview, EQ-5D and SF-12 information was collected. HRQoL information was available for 20 EUROASPIRE III countries: Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Finland, France, Greece, Ireland, Italy, Latvia, Lithuania, Poland, Romania, Russian Federation, Slovenia, Spain, The Netherlands, Turkey, and the United Kingdom (UK). Furthermore, self-reported demographic details as well as disease information were collected by trained research staff.

HRQoL instruments

EQ-5D is a commonly used, easy to complete, standardized instrument containing a descriptive part (EQ_{index}) and a visual analogue scale (EQ-VAS). The former covers 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with three response categories each (no problems, some problems, or severe problems). The answers on these dimensions provide a simple descriptive profile, with 243 possible health states, from which an index score can be calculated. Within the current analyses we have chosen to use the UK algorithm for all countries included. Conform with the EuroQoL guidelines we used this most robust valuation set, since country specific algorithms were not available for each individual country included. Theoretically, the index score can range between -0.594 (worst health state) and 1 (full health) (Rabin et al, 2001). The algorithm is based on the time trade off (TTO) technique developed by Torrance et al (Torrance, 1976). With this method, the subject can chose between two alternatives: a state of illness during a given period followed by death, versus a state of perfect health for a shorter time period, followed by death. The time period is varied until the subject is indifferent between the two alternatives.

The SF-12v2 is a shortened version of the SF-36, including 12 questions, with three to five answer categories each (Likert scale). The instrument covers eight dimensions: general health, physical functioning, role physical, bodily pain, vitality, social functioning, role emotional, and mental health. Both a physical (PCS-12) and mental functioning (MCS-12) component score, ranging between 0 and 100, can be calculated using a scoring algorithm. Lower scores represent worse and higher scores represent better self-perceived HRQoL outcomes (Ware et al, 2002). Using an algorithm (UK version) by Brazier et al. (2004), the SF-6D can be calculated from the SF-12. The SF-6D is based on 11 SF-12 questions and combines them into 6 dimensions (physical functioning, role limitations, bodily pain, vitality, social functioning, mental health); 7500 different health states can be defined, from which an index score can be calculated. The score can range between 0.296 and 1 (Brazier et al, 2004b; Kharroubi et al, 2007; McCabe et al, 2006). The algorithm to calculate this score is based on the standard gamble (SG) technique, first described by von Neumann and Morgenstern (Von Neumann & Morgenstern, 1994). It is based on a paired comparison in which subjects can chose between two alternatives. The first alternative has two possible outcomes, either the subject returns to perfect health with probability p, or the subject dies with probability 1-p. The second alternative leads to a certain disease state for life. The probability p can be varied until the subject is indifferent between the two alternatives. Due to the high number of different health states, many of them are not explicitly evaluated but estimated based on their proximity to those states which are tested.

Statistical analyses

Only patients with both EQ-5D and SF-12 information were included in the analyses. Analyses were performed both on European as well as on country-specific level. A Wilcoxon signed rank test was performed in order to test whether the EQ-5D results differ significantly from the SF-6D values. Furthermore, the spearman correlation and the intraclass correlation coefficient between EQ-5D and SF-6D outcomes, and the spearman correlation between the different dimensions of the EQ-5D and SF-6D were calculated. The ceiling effect of both measures was assessed by estimating the proportion of patients who reported to be in full health (no problems on either dimension). Analyses were performed using IBM SPSS version 21.

3. Results

A total of 7,472 coronary patients completed the SF-12 as well as the EQ-5D instrument. Their mean age was 63.1 (9.2) years. Three quarter of patients were male, and one in four patients had received a low education. Almost 60% had a cardiac revascularization as recruiting diagnosis; 23.2% of patients reported to suffer from diabetes; 4.5% reported to have a history of stroke and 13.3% reported to have suffered a recurrent coronary event since the recruiting diagnosis. Table 1 gives an overview of the utility outcomes based on the patient characteristics. Country specific results are presented in table 2. The median EQ-5D values range between 0.66 (Russia) and 1.00 (Italy) depending on the country. The lowest EQ-5D value reported was -0.59 and the highest value was 1.00. About 1.8% of patients had EQ-5D outcomes below 0, reflecting health states that are perceived worse than death. The median SF-6D values ranged between 0.66 (Spain, France, Croatia, Lithuania, Poland, Russia, Slovenia, Turkey) and 0.80 (Cyprus, Italy, the Netherlands), the lowest SF-6D value was 0.35 and the highest was 1.00.

The EQ-5D and SF-6D seemed to be significantly correlated with an overall spearman correlation coefficient of 0.695. The intraclass correlation coefficient, although significant, was somewhat lower with an overall value of 0.536. The correlation between the different HRQoL dimensions is reported in table 3. All dimensions were significantly correlated with each other. The highest correlations are seen between related dimensions such as physical functioning-mobility (r=0.446); physical functioning-usual activities (r=0.504); role limitation-usual activities (r=0.390); social functioning-usual activities (r=0.403); pain-pain/discomfort (r=0.630); mental health-anxiety/depression (r=0.551).

Table 1: Utility outcomes by patient characteristics

	EQ-5D (Median (IQR))	SF-6D (Median (IQR))
All	0.80(0.69-1.00)	0.70(0.62-0.82)
Gender		
Male	0.80(0.69-1.00)	0.72(0.63-0.86)
Female	0.73(0.62-0.85)	0.66(0.58-0.74)
Age		
<50 years	0.85(0.73-1.00)	0.72(0.64-0.86)
50-59 years	0.80(0.69-1.00)	0.72(0.62-0.86)
60-69 years	0.80(0.69-1.00)	0.70(0.62-0.83)
≥70 years	0.73(0.62-0.85	0.66(0.61-0.78)
Recruiting diagnosis		
CABG	0.80(0.69-1.00)	0.72(0.63-0.96)
PCI	0.80(0.69-1.00)	0.72(0.62-0.86)
AMI	0.78(0.66-1.00)	0.66(0.62-0.80)
Ischemia	0.73(0.62-0.88)	0.66(0.60-0.80)
Educational level		
primary	0.74(0.62-1.00)	0.66(0.606-0.80)
Secondary	0.80(0.69-1.00)	0.69(0.62-0.80)
High	0.81(0.73-1.00)	0.72(0.66-0.86)
Diabetes		
No	0.80(0.69-1.00)	0.72(0.62-0.86)
Yes	0.73(0.62-0.85)	0.66(0.60-0.78)
Central obesity		
No	0.81(0.69-1.00)	0.72(0.63-0.86)
Yes	0.74(0.64-0.85)	0.66(0.62-0.80)
Smoking		
No	0.80(0.69-1.00)	0.70(0.62-0.82)
Yes	0.80(0.66-1.00)	0.69(0.62-0.86)
Physical activity		
<20min, 3x/week	0.73(0.62-0.85)	0.66(0.60-0.78)
≥20min, 3x/week	0.80(0.69-1.00)	0.72(0.63-0.86)
History of stroke		
No	0.80(0.69-1.00)	0.70(0.62-0.82)
yes	0.69(0.52-0.85)	0.66(0.57-0.74)
Recurring coronary event after recruiting diagnosis		
No	0.80(0.69-1.00)	0.71(0.62-0.82)
yes	0.78(0.66-1.00)	0.66(0.62-0.80)

All EQ-5D and SF-6D outcomes are significantly different ($p<0.001$), except for patient with a history of stroke.

Overall 28.8% (2149/7472) of patients reported no problems on the EQ-5D instrument, whereas only 4.2% (311/7472) of patients reported full health on the SF-6D instrument.

Again some variation was seen across countries, with the proportion of full health on the EQ-5D instrument ranging from 10.4% (Russia) to 50.9% (Italy); on the SF-6D instrument full health was seen in 0.0% (Russia) to 15.7% (Cyprus) of patients depending on the country. In those patients with full health on the EQ-5D, a median SF-6D of 0.86 (IQR: 0.74-0.92) was found. Moreover 15.6% of patients with a full health on the EQ-5D still reported a SF-6D value below the overall median. Patients reporting no limitations on the EQ-5D still reported substantial problems on the SF-6D role limitation and vitality dimension.

Table 2: Country specific utility outcomes

	EQ-5D	SF-12	Wilc test	Spearman correlation	ICC	EQ-5D Full health	SF-12 Full health	Wilc test
	Median (IQR)					% (n)		
Overall (n=7472)	**0.80 (0.31)**	**0.70 (0.20)**	**	**0.665****	**0.536****	**28.8 (2149/7472)**	**4.2 (311/7472)**	**
Belgium (n=246)	0.81 (0.27)	0.72 (0.14)	**	0.595**	0.438**	39.0 (96/246)	2.0 (5/246)	
Bulgaria (n=538)	0.80 (0.34)	0.72 (0.25)	**	0.688**	0.593**	30.3 (163/538)	7.1 (38/538)	**
Cyprus (n=420)	0.85 (0.27)	0.80 (0.26)	**	0.621**	0.528**	37.6 (158/420)	15.7 (66/420)	**
Czech Rep (n=475)	0.76 (0.19)	0.72 (0.18)	**	0.636**	0.515**	24.8 (118/475)	1.3 (6/475)	**
Spain (n=473)	0.76 (0.34)	0.66 (0.20)	**	0.679**	0.512**	25.4 (120/473)	3.8 (18/473)	**
Finland (n=237)	0.80 (0.31)	0.72 (0.24)	**	0.644**	0.518**	29.1 (69/237)	3.0 (7/237)	**
France (n=269)	0.73 (0.18)	0.66 (0.14)	**	0.572**	0.430**	17.8 (48/269)	0.7 (2/269)	
UK (n=277)	0.80 (0.31)	0.72 (0.25)	**	0.720**	0.583**	29.6 (82/277)	2.2 (6/277)	*
Greece (n=119)	0.85 (0.31)	0.72 (0.20)	**	0.605**	0.513**	35.3 (42/119)	7.6 (9/119)	**
Croatia (n=437)	0.73 (0.23)	0.66 (0.17)	**	0.670**	0.518**	22.7 (99/437)	2.5 (11/437)	**
Ireland (n=370)	0.85 (0.27)	0.78 (0.21)	**	0.713**	0.620**	39.2 (145/370)	4.6 (17/370)	**
Italy (n=377)	1.00 (0.2)	0.80 (0.26)	**	0.634**	0.519**	50.9 (192/377)	4.5 (17/377)	**
Lithuania (n=505)	0.74 (0.19)	0.66 (0.18)	**	0.583**	0.464**	20.4 (103/505)	1.8 (9/505)	*
Latvia (n=518)	0.85 (0.27)	0.74 (0.23)	**	0.503**	0.422**	39.6 (205/518)	8.1 (42/518)	**
Netherlands (n=199)	0.85 (0.27)	0.80 (0.25)	**	0.664**	0.607**	42.2 (84/199)	10.1 (20/199)	**
Poland (n=461)	0.73 (0.23)	0.66 (0.14)	**	0.651**	0.489**	20.4 (94/461)	0.7 (3/461)	**
Romania (n=521)	0.76 (0.19)	0.68 (0.18)	**	0.649**	0.504**	24.6 (128/521)	3.3 (17/521)	**
Russia (n=405)	0.66 (0.15)	0.66 (0.14)	*	0.698**	0.494**	10.4 (42/405)	0.0 (0/521)	
Slovenia (n=292)	0.69 (0.33)	0.66 (0.15)	*	0.688**	0.485**	14.7 (43/292)	2.7 (8/292)	**
Turkey (n=333)	0.81 (0.31)	0.66 (0.13)	**	0.689**	0.456**	35.4 (118/333)	3.0 (10/333)	**

Wilc test: Wilcoxon Signed rank test
*p-value <0.05; **p-value<0.01

Furthermore, of those patients reporting full health on the EQ-5D, 15.5% of patients had a PCS-12 value below the overall median, and 23.0% had a MCS-12 value below the overall median. In contrast, in those patients with full health on the SF-6D only 4.2% of patients reported an EQ-5D value below the overall median. Patients with an EQ-5D value below 0, had SF-6D values ranging between 0.35 and 0.68. Only 1 patient reported severe problems on all the EQ-5D dimensions, whereas none of the patients reported the worst possible SF-6D health state.

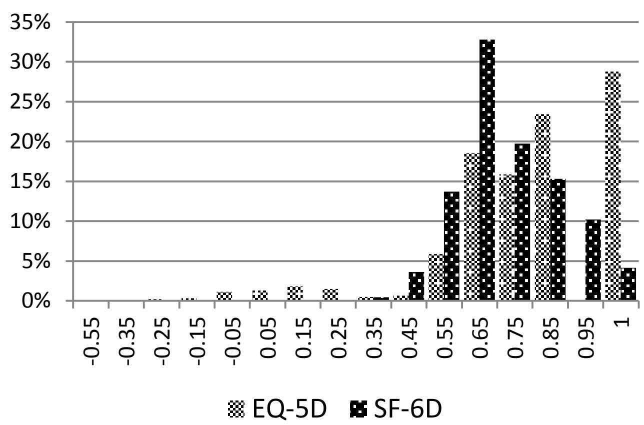
Figure 1 compares the EQ-5D utilities with the SF-6D utilities according to patient’s EQ-5D health profile. According to these data, patients with worse EQ-5D outcomes were more likely to have better SF-6D outcomes, whereas patients with better EQ-5D outcomes were more likely to have worse SF-6D results.

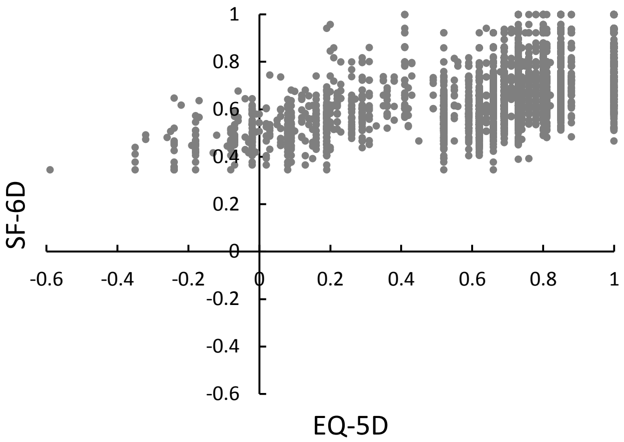
Table 3: Correlation between EQ-5D and SF-12 (SF-6D) dimensions

	Physical functioning	Role limitation	Social functioning	Pain	Mental health	Vitality
Mobility	**0.446**	0.338	0.346	0.459	0.268	0.325
Self care	0.318	0.223	0.313	0.321	0.230	0.247
Usual activities	**0.504**	**0.390**	**0.403**	0.474	0.321	0.371
Pain/discomfort	0.415	0.395	0.390	**0.630**	0.354	0.343
Anxiety/depression	0.281	0.405	0.410	0.338	**0.551**	0.324

All correlations are significant ($p<0.001$)

Figure 1: Comparison between EQ-5D and SF-6D utilities





4. Discussion

Similar to previous studies in various populations, the EQ-5D outcomes in coronary patients are significantly correlated with the SF-6D values, with ICC’s indicating moderate agreement between the instruments (Brazier et al, 2004a; Ferreira et al, 2008; Kontodimopoulos et al, 2011). Moderate correlations were also found between related dimensions. Correlations found in our study were slightly lower (with the exception of those related to pain and mental health) than those reported by Brazier et al (Brazier et al, 2004a), but stronger than those seen by Van Stel et al (van Stel et al, 2006). However, there remain significant differences between the EQ-5D and SF-6D utility outcomes. In all EUROASPIRE III countries, the utility values differed significantly from each other with median SF-6D utility scores being systematically lower than EQ-5D outcomes, both at country specific level, as well as after stratification by patient characteristics. Due to the small sample sizes on country specific level, and the variability in disease severity and comorbidities, caution is required when interpreting the results at country level. It should be noted also, that EQ-5D utility outcomes are based on UK preference weights, since country-specific weight were not available for all included countries. Furthermore, a ceiling effect was observed in the EQ-5D instrument, but no floor effect was seen on either instrument (although a slight proportion of patients reported EQ-5D outcomes below zero). These results are similar to previously reported outcomes (Joore et al, 2010; van Stel et al, 2006). One study reported on full health in the general population, with 47% of patients having no problems on the EQ-5D and 5.8% of patients reporting no problems on the SF-6D (Bharmal et al, 2006). According to a study by Joore et al. (2010) 40% to 54% of hypertensive patients (depending in the treatment modality) report full health on the EQ-5D, whereas only 1% to 2% reported no problems on the SF-6D (Joore et al, 2010). A study in coronary patients found a ceiling effect on the EQ-5D in 13.5%, whereas only 0.4% of patients reported full health on the SF-6D (van Stel et al, 2006). Brazier et al. acknowledge a possible ceiling effect of the EQ-5D$_{index}$ tool and a possible floor effect of the SF-6D instrument (Brazier et al, 2004a). Subanalyses in the EUROASPIRE III population revealed that patients reporting no problems on the EQ-5D still reported substantial problems on the SF-6D role limitation and vitality dimensions. This is in line with the lower correlations between the EQ-5D dimensions and the SF-6D role limitation and vitality dimension. Furthermore, within our population, especially mental problems are not completely captured by the EQ-5D instrument. Likewise, in the study by Brazier et al. (2004), based on 7 patient groups, it was observed that those patients in full health on the EQ-5D may still experience problems in physical functioning, mental health and vitality (Brazier et al, 2004a).

As mentioned by others, some of the differences between the instruments might be explained by the theoretical construction of the measures (Brazier et al, 2004a; Bryan et al, 2005; van Stel et al, 2006). First of all, EQ-5D contains only 5 dimensions, whereas SF-6D captures 6 dimensions. In addition, the recall period is different: ‘today’ versus ‘past four weeks’, however we agree with Van Stel et al. (2006), that the influence of the recall period in the utility differences might be non-significant, since HRQoL was measured in stable CHD patients (6 months to 3 years after the recruiting diagnosis) (van Stel et al, 2006). Furthermore, the EQ-5D covers only 5 dimensions with each 3 answer categories, whereas the SF-6D is based on 11 SF-12 questions with each 3 to 5 response categories. An increase in number of questions and answers automatically leads to a more descriptive and sensitive tool with a higher amount of possible outcomes. A patient who has sometimes frightened feelings, might for example indicate that he/she is not anxious or depressed on the EQ-5D whereas on the SF-12 he/she would indicate ‘a little of the time’ on the question whether he/she has felt downhearted and depressed. This is only one example indicating the more refined answer options of the SF-12. However, conversion from SF-12 to SF-6D is associated with some sensitivity loss, particularly due to the small range of possible utility scores. The SF-6D outcomes range between 0.296 and 1 which is almost half of the possible EQ-5D range, hence SF-6D outcomes are more centred to the middle and the potential difference between health states is larger using the EQ-5D utility scores. This was also reported in a paper by McDonough et al. (2007), concluding that cost-effectiveness analyses using the SF-6D give less favourable cost-effectiveness results (McDonough et al, 2007). The EQ-5D however, is very much skewed to the right, hence the probability of having worse outcomes is rather low, and therefore the room for improvement is limited especially in patients with a mild or largely asymptomatic condition. In contrast, the impairments associated with a mild condition might be better recognized by the SF-6D, hence the SF-6D might be more sensitive for smaller impairments, leading to better cost-effectiveness outcomes. Indeed, the change in utility score rather than the absolute value of the score is of most importance in cost-effectiveness analyses. In agreement with the literature, EUROASPIRE III results have indicated that patients with worse EQ-5D outcomes were more likely to have better SF-6D results, whereas patients with better EQ-5D outcomes were more likely to have worse SF-6D results (Joore et al, 2010). Furthermore, our results indicate that disease severity or patient characteristics are not always captured by both instruments equally. In patients with diabetes, a history of stroke or a recurrent coronary event, the proportion of patients reporting full health is lower, both using the EQ-5D as well as the SF-6D. However, patients who are categorized as having a CABG or PCI, were more likely to report full health on the EQ-5D but not on the SF-6D compared to patients having AMI or ischemia. Likewise, smokers and obese patients were less likely to report full health on the SF-6D but not on the EQ-5D compared to non-smokers and patients with a normal weight.

Medicine has changed tremendously during the last century. New scientific insights have led to the development of several innovations regarding medication, technical procedures and diagnostic tools. Today's society strives to provide the best possible health care, however financial resources are limited. Therefore, the use of cost-effectiveness analyses is becoming increasingly important. Current recommendations from NICE promote the use of the EQ-5D instrument for the calculation of QALYs (National Institute for Health and Care Excellence, 2013). However, it is important to recognize the advantages and disadvantages of both the EQ-5D and SF-6D instrument. Whereas the main disadvantage of the EQ-5D is its ceiling effect, the potential advantages of SF-12 might disappear when converting the outcomes into an SF-6D utility score. The new EQ-5D five level (EQ-5D-5L) might overcome some of the above reported problems by increasing sensitivity and reducing the ceiling effects, however further research is needed in order to investigate these issues (Herdman et al, 2011).

Furthermore, as both the EQ-5D as well as the SF-12 might be insufficiently sensitive to capture small differences in coronary patients, a disease-specific instrument from which a utility outcome can be calculated should be developed. Such a tool can significantly improve the reliability of health economic evaluations.

In conclusion, our study results have indicated that both utility tools are not interchangeable. In addition to the different theoretical construction of the instruments as well as the unequal utility range, differences in outcome can also be explained by patient characteristics and disease severity. Knowledge of these inconsistencies is required when using utility values, in order to avoid comparison of values derived from different instruments.

Chapter 9.
Cost-effectiveness of cardiovascular prevention

Based on:

De Smedt D, Kotseva K, De Bacquer D, Wood D, De Backer G, Dallongeville J, Seppo J, Pająk A, Reiner Ž, Vanuzzo D, Georgiev B, Gotcheva N, and Annemans L, On behalf of the EUROASPIRE study group

Cost-effectiveness of optimizing prevention in patients with coronary heart disease: the EUROASPIRE III health economics project.

European Heart Journal (2012); 33: 2865–72

Abstract

Aims: The EUROASPIRE III survey indicated that the guidelines on cardiovascular disease prevention are poorly implemented in patients with established Coronary Heart Disease (CHD). The purpose of this health economic project was to assess the potential clinical effectiveness and cost-effectiveness of optimizing cardiovascular prevention in eight EUROASPIRE III countries (Belgium, Bulgaria, Croatia, Finland, France, Italy, Poland, and the UK).

Methods and results: The individual risk for subsequent cardiovascular events was estimated, using published Framingham equations. Based on the EUROASPIRE III data, the type of suboptimal prevention, if any, was identified for each individual, and the effects of optimized tailored prevention (smoking cessation, diet and exercise, better management of elevated blood pressure and/or LDL-cholesterol) were estimated. Costs of prevention and savings of avoided events were based on country-specific data. A willingness to pay threshold of € 30,000/quality-adjusted life year (QALY) was used. The robustness of the results was validated by sensitivity analyses. Overall, the cost-effectiveness analyses for the eight countries showed mainly favourable results with an average incremental cost-effectiveness ratio (ICER) of € 12,484 per QALY. Only in the minority of patients at the lowest risk for recurrent events, intensifying preventive therapy seems not cost-effective. Also, the single impact of intensified cholesterol control seems less cost-effective, possibly because their initial 2-year risk was already fairly low, hence the room for improvement is rather limited.

Conclusion: These results underscore the societal value of optimizing prevention in most patients with established CHD, but also highlight the need for setting priorities towards patients more at risk and the need for more studies comparing intensified prevention with usual care in these patients.

1. Introduction

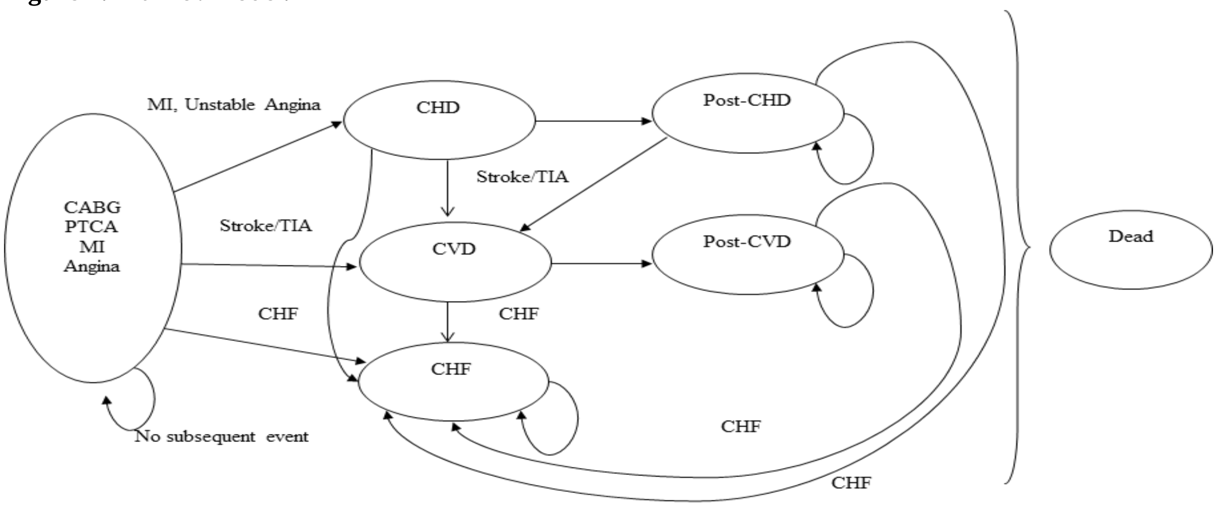
In 2008, >4.58 million people died in Europe due to cardiovascular diseases (CVD) (World Health Organisation, 2011). CVD continues to be the main cause of morbidity and mortality, with >30% of life-years lost and nearly half of all deaths (Allender et al, 2008). Consequently, CVD adds significantly to the increasing healthcare costs. According to Leal et al. the economic burden of CVD in the EU amounts to € 169 billion annually; 62% of these costs are healthcare-related. Per 1000 people, 2.4 working-years are lost due to mortality and 591 days are lost because of morbidity; representing a total EU cost (in 2003) of € 24,384 million and € 10,768 million, respectively. In addition, informal care of CVD patients was estimated to cost € 29,050 million yearly (Leal et al, 2006). During the previous decades several guidelines on cardiovascular prevention have been published. The first Joint European guidelines on the prevention of CVD in clinical practice were published in 1994 with regular updates since (De Backer et al, 2003; Graham et al, 2007; Pyorala et al, 1994; Wood et al, 1998). Within the European Society of Cardiology (ESC), secondary prevention was given the highest priority. Therefore, the ESC conducted three surveys (European Action on Secondary and Primary Prevention by Intervention to Reduce Events-EUROASPIRE) to ascertain whether the guidelines are being implemented in clinical practice (Kotseva et al, 2009b; EUROASPIRE Study Group, 1997; EUROASPIRE II Study Group, 2001). In the latest survey (EUROASPIRE III) many coronary patients still did not achieve the targets for CVD prevention, indicating that the integration of the guidelines in routine clinical care is still substandard. Hence there is considerable room for improvement to raise the standards of prevention in these patients through more effective lifestyle interventions, control of risk factors, and appropriate use of cardio protective medication. Optimizing the management of these coronary heart disease (CHD) patients would decrease the occurrence of subsequent CVD events, hence increasing their quality of life and extend their survival. Many studies already reported on the cost-effectiveness of single prevention strategies (Chen et al, 2009; Heeg et al, 2007; Lindgren et al, 2007; Lowensteyn et al, 2000; Soini et al, 2010; Taylor et al, 2009; Wilson et al, 2011). However, none conducted an integrated tailor-made cost-effectiveness analysis on secondary cardiovascular prevention targeting different intervention strategies simultaneously, adapted to the current prevention status of patients. This paper reports on the cost-effectiveness of such optimized prevention in cardiovascular patients in eight European countries, using the EUROASPIRE III data.

2. Methods

European cardiovascular disease prevention model

An individual-based state-transition model was designed to quantify the clinical and cost-effectiveness of optimizing secondary prevention. Opposed to common Markov models, based on a cohort with an average risk profile and average transition probabilities, the current model allows simulating the health and economic outcomes of individual patients taking into account their individual characteristics and their prevention status. The model makes use of 6-month cycles and includes three disease states, two post-event states, and a death state, and was developed after exploring the literature (Figure 1) (Heeg et al, 2007; Soini et al, 2010). All EUROASPIRE III patients start in the initial state. The model predicts their likelihood to develop fatal and non-fatal CVD or to die from other causes. Every cycle, patients can suffer a coronary event, a stroke, or heart failure and move to the CHD state, CVD state, or congestive heart failure (CHF) state, respectively. Once in one of these subsequent event states, patients enter a post-event state after one cycle.

Figure 1: Markov model.



All patients start in the coronary artery bypass graft (CABG)/percutaneous transluminal coronary angioplasty (PTCA)/myocardial infarction (MI)/angina disease state. Patients suffering a MI will move to the coronary heart disease state (CHD). Patients suffering a stroke will move to the cardiovascular disease state (CVD), patients suffering a heart failure will progress to the congestive heart failure state (CHF).

EUROASPIRE III survey

The design and the principal findings of the EUROASPIRE III survey have been reported extensively elsewhere (Kotseva et al, 2009b). In brief, the study aimed to determine whether the joint European guidelines on CVD prevention are being implemented in CHD patients at that time (De Backer et al, 2003). The survey was conducted in 22 European countries during 2006–07. Patients were aged 18–80 years and admitted to a hospital for an acute coronary event or a cardiac procedure [i.e. coronary artery bypass graft (CABG); percutaneous transluminal coronary angioplasty (PTCA), myocardial infarction (MI), or acute myocardial ischemia]. EUROASPIRE patients from eight countries were included in our analysis (Bulgaria, Belgium, Croatia, Finland, France, Italy, Poland, and the UK). Depending on the country only 3–43% of patients are meeting all targets, i.e. achieving blood pressure (BP) target, cholesterol target, physical activity target, and smoking target. In total 2693 patients not on target on at least one of the risk factors were included in our study.

Base case risk and risk reductions

Performing a tailor-made analysis necessitates the calculation of individuals' future cardiovascular risk. From all available risk prediction algorithms, such as SCORE, QRISK, PROCAM, ASSIGN, LIPID, reynolds risk score, UKPDS etc. The Framingham risk equations were used to calculate the different CVD outcomes since these allow risk estimation based on individual patient risk factors, collected within the EUROASPIRE III survey (D'Agostino et al, 2000; Kannel et al, 1999; Wolf et al, 1991). However, evidence indicates that the Framingham risk calculators might overestimate CVD risk; in addition the Framingham population differs in characteristics from the EUROASPIRE population. Therefore, in order to use the Framingham risk calculators, calibration was applied based on mean CHD, stroke, and CHF risk figures available in the literature (Alberts et al, 2009; Hense et al, 2003; Kober et al, 1995; Pedersen et al, 2005). If the figures in the literature differed from our calculated risk, based on the mean of the individual patient calculations, then our individual patient calculations were multiplied with a correction factor in order to have the same overall risk figure as those reported in a typical European CHD population.

Optimizing prevention

Optimizing prevention was based on the 2003 joint European guidelines (De Backer et al, 2003). In those patients not on target, several strategies were theoretically applied in order to improve their risk factors and consequently their cardiovascular risk. Hence their future risk was calculated assuming optimized risk target treatment. About 17% of the patients included in our analyses were smokers. Optimal smoking cessation was installed through counselling and pharmacotherapy [varenicline or nicotine replacement therapy (NRT)]. Fifty-two per cent of the patients had a total cholesterol not on target. Simvastatine 20 mg per day was initiated in patients with an elevated total cholesterol of ≥4.5 mmol/L and not yet receiving cholesterol treatment. It was assumed that in those ≤6% above target it was an issue of improving compliance. In patients with a cholesterol level between 6 and 12% above target, the statin dose was doubled if possible and atorvastatine 40 mg/day was given if patients were already on the maximum dose of a weaker statin (type fluvastatin, lovastatin, pravastatin, or simvastatin). Ezetimibe was added in patients already on a maximum dose of a strong statin (type atorvastatin or rosuvastatin). This was based on the literature indicating a 6% additional fall in the risk factor level by doubling the dose (Weng et al, 2010). An elevated BP was found in 60% of patients. Those with a raised BP (BP >140/90 mmHg and BP >130/80 mmHg for CHD patients without diabetes, and with diabetes, respectively) and not yet on treatment were placed on one inexpensive antihypertensive drug, (e.g. beta-blocker or diuretic). For those with a slightly increased BP (BP >140/90 and <150/95 mmHg for non-diabetics and BP >130/80 and <140/90 mmHg for diabetics), but already on treatment, a compliance problem was assumed. When the BP exceeded 150/95 and 140/90 mmHg, respectively, in non-diabetics and diabetics already on treatment, a combination therapy was installed with a maximum of four different BP-lowering drugs. Regarding physical activity a lifestyle intervention was implemented in 77% of patients because they were not regularly physical active.

Calculation of the risk reduction

Optimizing the preventive actions in coronary patients leads to a reduction in cardiovascular events. Relative risks (RRs) related with these preventive actions were gathered from metaanalyses or large clinical trials (Table 1) (Clark et al, 2005; Critchley et al, 2003; Frey et al, 2011; Kjekshus et al, 1997; Mills et al, 2011b; Mills et al, 2011a; Shah et al, 2010; Spector et al, 2011; Turnbull et al, 2005). Note that the risk reduction associated with smoking cessation was based on the effect of the smoking cessation therapy, accounting for the willingness to quit and the yearly relapse rates (Wetter et al, 2004).

Table 1: Relative risks associated with different interventions to optimize prevention

Intervention		CHD	Stroke	CHF
Smoking cessation		0.68 (0.57-0.82) (Critchley et al, 2003)	0.68 (0.54-0.85) (Frey et al, 2011)	0.68 (0.47-0.99) (Critchley et al, 2003)
Cholesterol-lowering medication	Standard vs. no therapy	0.82 (0.75-0.91) (Mills et al, 2011b)	0.86 (0.78-0.95) (Mills et al, 2011b)	0.79 (0.63-0.95) (Kjekshus et al, 1997)
	Intensive vs. standard therapy	0.9 (0.84-0.96) (Mills et al, 2011a)	0.85 (0.76-0.97) (Spector et al, 2011)	0.9 (0.84-0.96) (Mills et al, 2011a)
Blood pressure-lowering medication	Standard vs. no therapy	0.8 (0.73-0.88) (Turnbull et al, 2005)	0.72 (0.62-0.83) (Turnbull et al, 2005)	0.82 (0.69-0.98) (Turnbull et al, 2005)
	Intensive vs. standard therapy	0.95 (0.78-1.16) (Turnbull et al, 2005)	0.76 (0.58-1) (Turnbull et al, 2005)	0.82 (0.55-1.22) (Turnbull et al, 2005)
Physical activity		0.62 (0.44-0.87) (Clark et al, 2005)	0.55 (0.39-0.77) (Clark et al, 2005)	0.62 (0.44-0.87) (Clark et al, 2005)

These RRs indicate the effect of targeting one risk factor; however, in reality many patients have multiple risk factors not on target. Within our cohort, 41.3% of patients included in the analyses had two risk factors, 26.2% had three risk factors and 4.2% had all four risk factors not on target. Optimizing prevention implies addressing these risk factors simultaneously. Adding up the individual risk reduction would result in an overestimation of the total risk reduction, therefore, when multiple interventions are initiated a correction was made: $1 - ((1 - RR1 \times RR2) \times 0.8)$. The equation was formulated by comparing the effect of controlling multiple risk factors simultaneously vs. controlling individual risk factors separately (Dagenais et al, 2006). Country, age, and gender-specific general mortality probabilities were derived from WHO data (World Health Organisation, 2011). Cardiovascular mortality rates were based on data published by Vaartjes et al (Vaartjes et al, 2010).

Cost of optimized prevention

Optimizing prevention involves additional country-specific treatment costs for the health-care sector (Table 2). For smoking cessation, the cost of a 12 week drug treatment was considered, supplemented with the cost of two cardiologist visits and three motivational support visits. Regarding cholesterol and BP treatment daily medication and two yearly cardiologist visits were accounted for. These visits were assumed to increase adherence with the treatment. The lifestyle intervention to increase physical activity included individual sessions, group sessions, and a fitness programme (Jacobs-van der Bruggen MA et al, 2007).

Cost of avoided events

Effective prevention should lead to a decrease in the number of cardiovascular events and therefore the health-care costs associated with these events will decrease. Country-specific data were gathered by the national coordinators to estimate these costs (Table 3).

Quality of life

The main outcome is expressed as quality-adjusted life years (QALYs). QALYs combine the quantity and quality of life, whereby the latter is represented by a utility value varying between 0 (death) and 1 (perfect health). To calculate the total QALYs associated with a given condition, the utility value is multiplied with the expected number of life years spent in that condition. The EUROASPIRE III database contains utility values for each patient during his initial disease state. A subsequent coronary event was assigned a penalty value of 0.0578 for the remainder of the model, whereas stroke and CHF are appointed the penalty value 0.2743 and 0.1372, respectively (Saarni et al, 2006; Schwander et al, 2009).

Table 2: Country-specific intervention cost (€)

	Cholesterol treatment/day (range)	Blood pressure treatment /day (range)	Smoking cessation treatment /year (NRT/varenicline)	Lifestyle intervention /year [f]
Belgium	0.19-1.59 [a]	0.18-0.30 [a]	384/407 [a]	329
Bulgaria	0.03-0.96	0.03-0.24	265/-	121
Croatia	0.07-1.34	0.07-0.15	154/907	168
Finland	0.49-1.45	0.15-0.49	466/571	319
France	0.32-1.82	0.17-0.44	370/509	298
Italy	0.07-1.84 [b]	0.17-0.42 [b]	312/560 [c]	279
Poland	0.05-1.48 [d,e]	0.05-0.15 [d]	67/301[d]	173 [d]
UK	0.81-1.87	0.05-0.81	662/718	309

[a] Gecommentarieerd Geneesmiddelenrepertorium. http://www.bcfi.be/; [b] Regione Emilia Romagna. http://www.saluter.it/documentazione/ptr/elaborati/129_ace_inibitori.pdf; [c] Federazione nazionale unitary di farmacia. http://www.federfarma.it; [d] Medycyna Praktyczna. http://www.mp.pl; [e] National Health Fund Poland. http://www.nfz.gov.pl; [f] (Jacobs-van der Bruggen MA et al, 2007); Bulgaria: IMS retail data; Croatia: Croatian National Health Insurance Institute data; Finland: Official Finnish medical agency prices.

Cost-effectiveness

An incremental cost-effectiveness ratio (ICER) defined as the ratio between the net total costs and the net effects expressed in QALYs was calculated:

$$\frac{\text{(Cost optimized prevention – Cost current prevention)}}{\text{(Effectiveness optimized prevention – Effectiveness current prevention)}}$$

Sensitivity analyses

Health economic modelling entails uncertainty around the input parameters, therefore sensitivity analyses were performed. Each input parameter is assumed to vary within a range of possible values defined by their probability distribution, based on standard error estimates from the literature (if not available a ±30% range was used). Moreover, different scenarios were tested such as the use of NRT vs. varenicline, Framingham calibration vs. no calibration and applying an adjustment when combining the individual risk reduction vs. no adjustment. In addition, a cost-effectiveness acceptability curve estimating the probability that the results are cost-effective at different willingness to pay thresholds was calculated.

Table 3: Country-specific cost of diseases (€)

	BELGIUM	BULGARIA	CROATIA	FINLAND	FRANCE	ITALY	POLAND	UK
CHD (acute cost)	6178 [a]	2108	4000	6400	4337	6200 [c]	2077 [e]	1599 [f]
CHD (first 6 months after the event)	2660 [a]	442	3000	3215	1850	4200 [c]	501 [e]	1333 [g]
CHD (Second and further 6 months after acute event)	1197 [a]	442	1250	708	1850	1800 [c]	430 [e]	1333 [g]
Stroke (acute cost)	7366 [a]	1423	2500	6500	5029	3926 [d]	1365 [e]	2830 [f]
Stroke (first 6 months after the event)	3712 [a]	220	4530	8610	4821	2500 [d]	4164 [e]	1263 [g]
Stroke (Second and further 6 months after acute event)	2591 [a]	256	4150	2000	4821	1500 [d]	1014 [e]	1263 [g]
Clinical heart failure	1444 [b]	189	1856	4000	1021	2948 [d]	1859 [e]	1618 [f]

a (Annemans et al, 2003); b (Muls et al, 1998); c (Mantovani et al, 2009); d (Morsanutto et al, 2005); e (National Health Fund Poland, www.nfz.gov.pl.); f (NHS Department of Health., https://www.gov.uk/government/publications/reference-costs-guidance-for-2012-13--2); g (Flack et al, 2007); Bulgaria: 2010 contract between Ministry of Health and National Health Fund; Croatia: Croatian National Health Insurance Institute data; Finland: KELA-Social insurance institute of Finland; France: hospital data and reimbursement data.

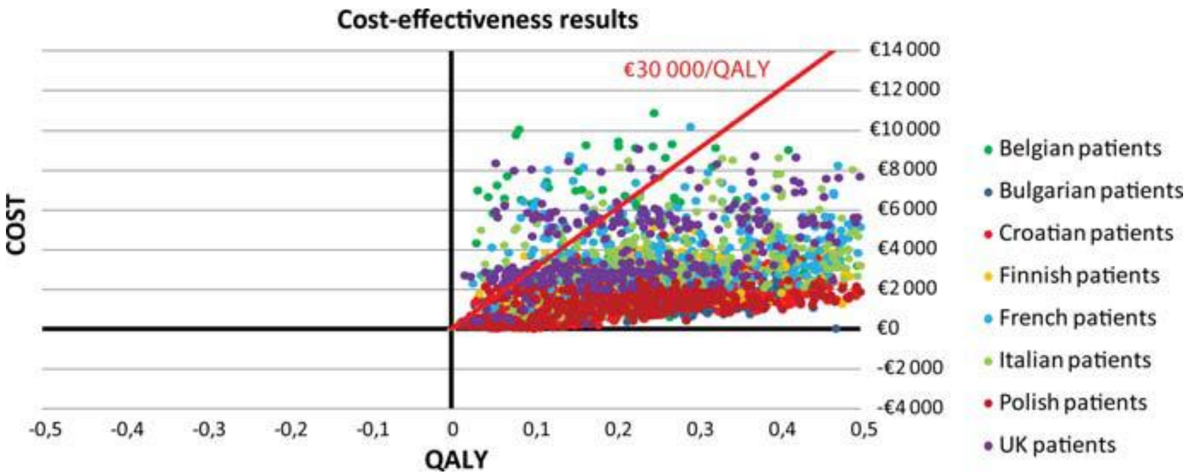
3. Results

Base case scenario

Assuming a 10-year time horizon, a time period often used in CVD prediction (Annemans et al, 2007), analyses revealed a higher QALY increase of 0.25 compared with the current situation; corresponding with three additional months in perfect health. Likewise optimizing prevention is associated with a mean cost increase of € 2493 per patient, resulting in an overall cost-effectiveness ratio of € 12,484/QALY (Figure 2).

These results differ between countries with lower ratios for Bulgaria (€ 7029/QALY), Poland (€ 7161/QALY), Croatia (€ 8406/QALY) and higher ratios for Finland (€ 11,660/QALY), Italy (€ 14,627/QALY), France (€ 6939/QALY), Belgium (€ 19,862/QALY), and the UK (€ 23,491/QALY) (Table 4).

Figure 2: Cost-effectiveness results



Results of cost-effectiveness analyses on individual patient data represented in a cost-effectiveness plane. The red diagonal line indicates a willingness to pay threshold of €30,000/QALY

Table 4: Country-specific mean incremental cost, incremental effect, and incremental cost-effectiveness ratio (ICER)

Country	Mean Incremental effect (QALY)	Mean Incremental cost (€)	Mean ICER (€/QALY)
Belgium	0,25	3200	19,937
Bulgaria	0,23	1297	6866
Croatia	0,25	1626	8478
Finland	0,25	2427	11,678
France	0,29	3790	16,970
Italy	0,29	3373	14,671
Poland	0,20	1175	6922
UK	0,23	3970	23,666

Result according to risk profile

As shown in Figure 3, a better cost-effectiveness is more likely to occur in patients with a higher cardiovascular risk. Patients with a 2-year risk estimation <5% have a mean ICER of € 24,862/ QALY, whereas the ICER of patients with a 2-year risk between 5 and 10% equals € 12,630/QALY. Those with a 2-year risk exceeding 10% have a mean ICER of € 7,844/QALY. Several factors contribute to this relationship. The mean ICER improves with increasing age varying from € 26,816/QALY for those <50 years old to € 8786/QALY for those >65 years of age. The ICER is the highest in those patients with a single cholesterol problem (ICER = € 26,069/QALY) and the lowest in those only in need for BP treatment (ICER =€ 9108/QALY). Subanalyses reveal a low gain in QALY in smokers and high cholesterol patients (0.024 and 0.071 QALY, respectively). On the contrary, the physical activity and BP-lowering interventions are associated with a high incremental effect (0.22 and 0.13 QALY, respectively). Similar but more moderate results were found for patients with more risk factors not on target (Table 5).

Figure 3: Cost-effectiveness results in function of the risk status.

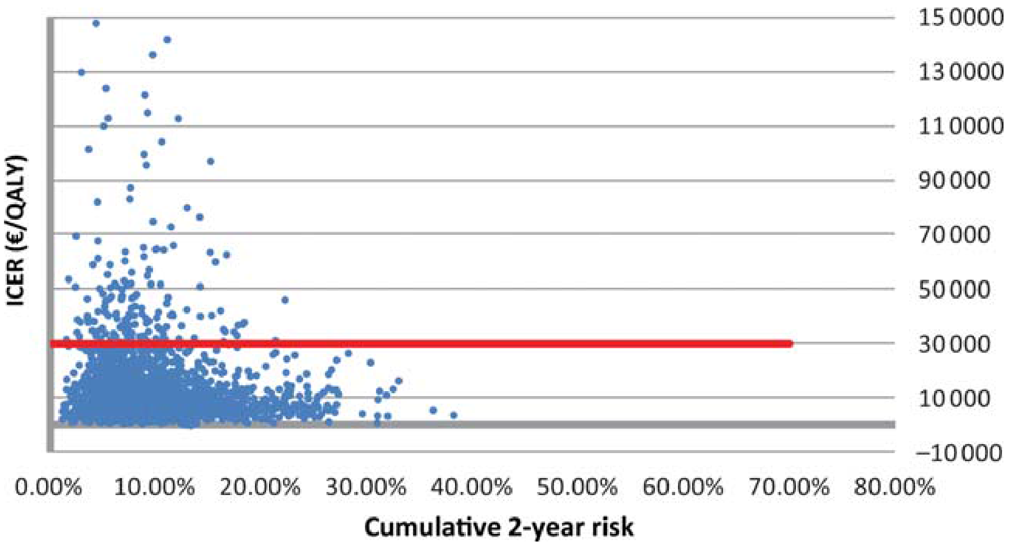


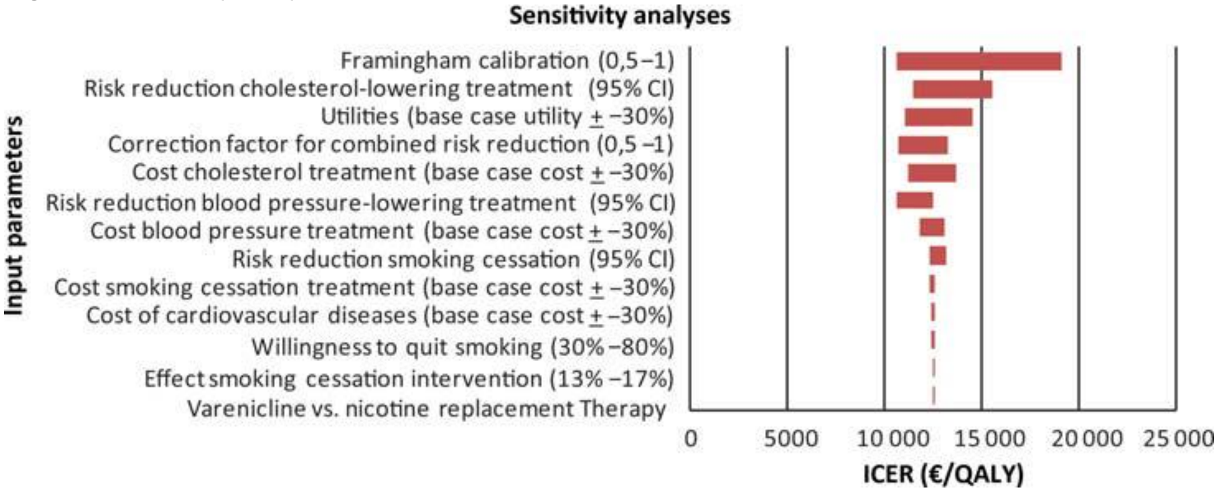
Table 5: Results according to subgroup classification

Risk profile	*ICER*
Patients <50 years old	€ 26,759/QALY
Patients <60 years old	€ 17,920/QALY
Patients <65 years old	€ 15,638/QALY
Patients >65 years old	€ 8794/QALY
1 risk factor not on target	€ 12,627/QALY
2 risk factors not on target	€ 11,695/QALY
3 risk factors not on target	€ 13,165/QALY
4 risk factors not on target	€ 14,924/QALY
Single risk factor: Cholesterol elevated	€ 24,369/QALY
Single risk factor: Smoking	€ 14,694/QALY
Single risk factor: Blood Pressure elevated	€ 9086/QALY
Single risk factor: Physical inactivity	€ 10,553/QALY
Multiple risk factors: Cholesterol among others	€ 14,825/QALY
Multiple risk factors: Smoking among others	€ 15,102/QALY
Multiple risk factors: Blood Pressure among others	€ 11,033/QALY
Multiple risk factors: Physical inactivity among others	€ 11,775/QALY

Sensitivity analyses

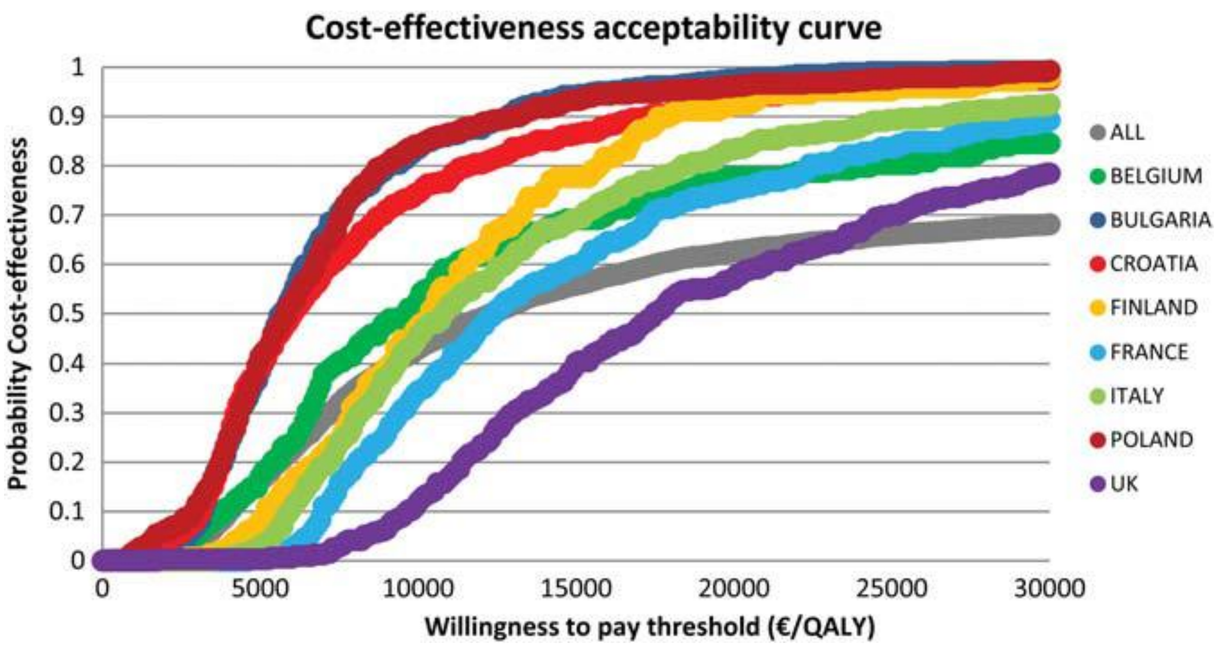
The results of the sensitivity analyses are presented in a Tornado diagram (Figure 4). The cost-effectiveness result was mainly sensitive for changes in the Framingham risk calibration, changes in the risk reduction following cholesterol-lowering therapy and changes in utility values. In addition, the method for calculating the total risk reduction, the costs related to cholesterol-lowering and BP-lowering treatment and the changes in the risk reduction following BP-lowering therapy and smoking cessation were of importance. The cost-effectiveness acceptability curve clearly shows a higher cost-effectiveness probability at a lower threshold for Bulgaria, Croatia, and Poland, compared with the other countries (Figure 5). At a threshold of 30,000€/QALY, optimizing prevention in the UK and Belgium have the lowest probability of being cost-effective (80%).

Figure 4: Sensitivity analyses



Tornado diagram based on uncertainty around input parameters

Figure 5: Cost-effectiveness acceptability



The cost-effectiveness acceptability curve for each individual country indicates the probability that the intervention is cost-effective given a range of willingness to pay thresholds.

4. Discussion

The EUROASPIRE III survey has shown a considerable potential to improve preventive strategies in order to achieve risk factor targets (EUROASPIRE Study Group, 1997). The current study evaluates the cost-effectiveness of optimizing tailor-made cardiovascular prevention in coronary patients. Overall, we found that optimizing secondary prevention is cost-effective compared with the current degree of cardiovascular prevention with an ICER of € 12,484/QALY. A willingness to pay threshold of € 30,000/QALY is commonly used. For Poland, Bulgaria and Croatia a lower threshold should be applied based on their gross domestic product (GDP) (World Health Organisation, 2001). Incremental cost-effectiveness ratios below the willingness to pay threshold are called cost-effective because the effectiveness of the intervention exceeds that of the current situation, however, at an additional cost. Results differed considerable between countries ranging from € 7029/QALY to € 23,491/QALY and were mainly driven by the country-specific costs. These results are consistent with the GDP of the eight countries with Bulgaria, Poland, and Croatia having a GDP of € 10,700, € 15,300, and € 14,800 per capita, respectively, whereas Belgium, Finland, France, Italy, and the UK have a GDP between € 24,000 and € 30,000 per capita (EUROSTAT, 2011). To our knowledge this is the first cost-effectiveness analysis on optimized, integrated, and tailor-made prevention. In the past, several studies have been published focusing on single (risk) factors and comparing prevention vs. no prevention. A recent study investigated the cost-effectiveness of a smoking cessation programme based on varenicline in smokers with CVD. Promising results were found with ICERs ranging between € 5151 and € 6120 per QALY gained (Wilson et al, 2011). A recent paper, based on the treating to new targets study investigating the cost-effectiveness of 80 mg atorvastatin vs. 10 mg atorvastatin found ratios of € 9500, € 21,000, and € 15,000 per QALY for UK, Spain, and Italy, respectively (Taylor et al, 2009). Likewise, Soini et al. evaluated the cost-effectiveness of atorvastatin (20 mg), rosuvastatin (10 mg), simvastatin (40 mg) and the combination of simvastatin (40 mg) with ezetimibe (10 mg) as secondary prevention strategy, reporting analogous results (Soini et al, 2010). Lindgren et al. reported on the cost-effectiveness of high dose atorvastatin compared with regular dose simvastatin based on the results from the IDEAL trial (Lindgren et al, 2007). The predicted ICER ranged between € 25,210 and € 62,639. Regarding antiplatelet medication an ICER of $ 36,343/QALY was found for clopidogrel plus aspirin vs. aspirin alone (Chen et al, 2009). A comprehensive review by Heeg et al., including 21 studies, reported that aspirin dominates placebo in secondary prevention as it has both a greater effectiveness and a lower cost (Heeg et al, 2007). A Canadian study examined the cost-effectiveness of exercise training for the secondary prevention of CVD and reported ICERs around $ 15,000 per life year saved (Lowensteyn et al, 2000). Subanalyses of our results revealed a better cost-effectiveness probability in higher risk patients, because of their larger room or improvement due to more potentially preventable events. Hence a greater absolute risk reduction can be established with similar intervention investments. Optimizing prevention seems particular cost-effective in elderly patients, and in those patients with a high BP or patients not physically active. Previous studies came to similar conclusions indicating the patients' level of risk being inversely correlated with the cost-effectiveness ratio (Heeg et al, 2007; Lindgren et al, 2007; Probstfield, 2003). Some assumptions and limitations of the study should be accounted for when interpreting the results. First, the Markov model includes only three CVD states whereby each subsequent event can only occur once per patient, potentially leading to an underestimation of the costs and an overestimation of QALY's both for optimized and current prevention, therefore in reality, optimizing prevention might be associated with a greater health gain. Furthermore, potential savings not related to CVD events were not considered. Secondly, our study used Framingham risk equations to estimate the subsequent CHD risk, stroke risk, and heart failure risk. However, the Framingham population has other characteristics than the EUROASPIRE population; furthermore, the data are from an era with little or no revascularization and with available medicines very different from nowadays. However, other available equations to estimate CHD, stroke, and CHF risk where not deemed appropriate because they only predict mortality, because they are based on patient characteristics not collected within EUROASPIRE III, or because they cannot be used in CHD patients. In order to account for the abovementioned shortcomings associated with the Framingham equations, a calibration was applied. Furthermore, with the exception of ageing of patients, typical changes in individuals' risk factors due to time progression were not accounted for. In addition, average European age-specific regional mortality figures where used, despite the differences in the cardiovascular death rate throughout Europe (Markovic et al, 2005). Thirdly, assumptions were made with regard to optimizing treatment. For risk factors close to target a compliance problem was assumed which could be resolved by increasing the number of cardiologist visits. For risk factors with values further away from target, optimized prevention consisted of a dose increase or the addition of a supplementary drug. Fourthly, some assumptions were made regarding the risk reductions. For those strategies for which no RR was available an extrapolation was conducted. To estimate the risk reduction associated with a combination of preventive actions individual risk reduction cannot simply be added or multiplied, since this would induce an overestimation of the total health gain. Therefore a formula was calculated taking into account a correction factor which was estimated from existing literature (Dagenais et al, 2006; Sanz et al, 2009; Yusuf et al, 2004). In addition, no age-related difference in the risk reductions was applied. It might be, however, that older patients, for example, benefit less from a physical activity intervention than younger patients (Lowensteyn et al, 2000). Furthermore, losses in the quality of life inherent to the intervention, for example the patients' perspective of losing the quality of life due to the fact that he is not allowed to smoke anymore, or due to statin side effects, were not accounted for. Moreover, it should also be noted that the quality of life measure used can greatly influence the calculated QALYs and hence overall ICER result. In this study we made use of EQ-5D utility values, however the use of SF-6D utilities for example would result in other outcomes (De Smedt, 2013c). Finally, cost data were provided by local coordinators, hence although several attempts made to minimize heterogeneity between data input, there is no complete certainty on consistency between countries. In conclusion, this tailor-made model on integrated secondary prevention in Europe is to our knowledge the first attempt to assess the cost-effectiveness of optimized tailor made and integrated prevention. Overall, optimizing prevention is cost-effective based on the EUROASPIRE III data. The best results are found in elderly and in patients with a high BP or in patients not physically active. Introducing preventive treatment actions in CHD patients should be based on their individual risk level since this is a key driver for cost-effectiveness.

Chapter 10.
General discussion

10.1 INTRODUCTION

The goal of today's medicine is not merely to improve patient survival but also to ensure that they achieve the best possible health-related quality of life (HRQoL). In essence HRQoL captures a person's self-perceived impact of a medical condition, its symptoms and its treatment (Schipper et al, 1996). Despite the extensive use of the concept, consensus is lacking on the definition of HRQoL. The term is used to describe a variety of concepts, such as functioning, health status, perceptions, life conditions, behaviour, happiness, lifestyle, symptoms etc. (Simko et al, 1999), therefore HRQol is sometimes referred to as an umbrella term (Feinstein et al, 1987). Although not quite the same, HRQoL and health status or functional status are often used interchangeably. Knowledge about HRQoL has increased over the years, changing concepts and definitions. Depending on the setting (scientific purpose, clinical practice, physicians, sociologists, psychologists, health economists, etc.) the concept is being used in different ways. However, the importance of HRQoL -in all it different meanings- is well-accepted. Depression, anxiety as well as functional status and general health perceptions have been shown to act as a predictor of future cardiovascular outcomes and mortality among coronary heart disease (CHD) patients (Agewall et al, 2012; Burstrom et al, 2001; DeSalvo et al, 2006; Kato et al, 2011; Pedersen et al, 2007; Spertus et al, 2002;

Thombs et al, 2008). Hence, tackling depressive and anxious feelings as well as impaired self-perceived health status and other HRQoL issues are of particular importance to the patients, their family as well as to health care providers and health care policy decision makers. In order to set up interventions addressing these issues, it is necessary to investigate the risk factors that are associated with worse HRQoL outcomes.

The general aim of this thesis was to focus on HRQoL/psychological distress among stable coronary patient, using the EUROASPIRE III (EUROpean Action on Secondary and Primary Prevention through Intervention to Reduce Events) database.

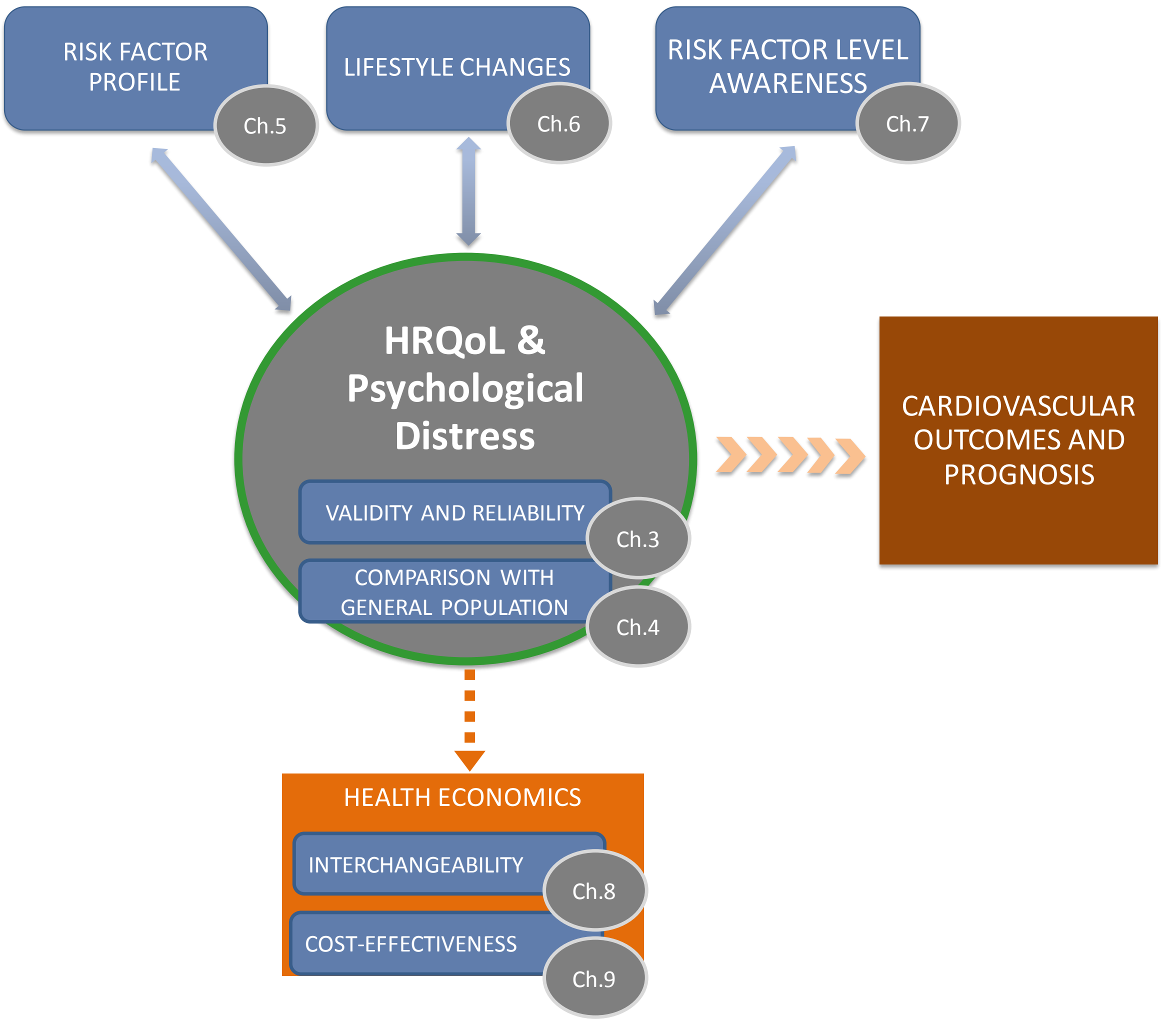


Figure 1: Research questions addressed within this thesis. The blue rounded squares indicate the investigated topics. The pink arrow shows what is already known from the literature. The dotted orange line indicates how HRQoL can be used in practice.

The EUROASPIRE III survey has several strengths including its large sample size and the inclusion of patients from 22 different European countries. Furthermore, data collection is not only based on abstracted medical record data but included face-to-face interviews and examinations using standardized methods and instruments, including central laboratory analyses of lipids and glucose. The median time interval between hospital admission and interview reached 1.24 years, allowing patients and health care providers to meet the proposed guideline standards. At the time of the interview, the acute CHD stage had passed and patients were likely to be in a more stable phase of the disease. In addition to risk factor assessment and questions about lifestyle changes, the interview questionnaire contained three tools to collect information about HRQoL/psychological distress: the EuroQoL 5 dimensions (EQ-5D), the 12-item short form health survey (SF-12) and the Hospital Anxiety and Depression Scale (HADS).

First, we investigated whether the instruments used were valid and reliable for use in a population of stable coronary patients (chapter 3). Some studies have already performed psychometric analyses of these instruments in CHD patients, however often in a smaller sample, or in a sample of patients with HRQoL data collected shortly after their acute coronary event (Ellis et al, 2005; Failde et al, 2010; Schweikert et al, 2006; Barth et al, 2005; Cosco et al, 2012). The EUROASPIRE III database allowed us to assess the reliability and validity of EQ-5D, SF-12 and HADS, based on a unique sample of 8745 stable CHD patients. Furthermore, we were able to compare the results across countries. The interpretation of the outcomes is difficult, if not impossible, in the absence of reference values from the general population. Hence, EQ-5D results from the EUROASPIRE III sample were compared with published normative values (chapter 4).

Several risk factors are well-known predictors of future cardiovascular outcome and mortality, both in the general population as well as in coronary patients (Canto et al, 2011; Conroy et al, 2003; Perk et al, 2012; Wilson et al, 1998). In the current thesis, we distinguish four risk factor categories (Gaziano et al, 2001). First there are the non-modifiable predisposing risk factors such as age, gender, family history, genetic predisposition, educational level and socio-economic status. Secondly, metabolic risk factors exist such as an elevated total cholesterol (TC), a high blood pressure (BP), diabetes, overweight and obesity. Thirdly, behavioural risk factors, such as smoking, lack of physical activity, an unhealthy diet and excessive alcohol intake are known CHD risk factors. And finally psychosocial factors such as stress, anxiety and depression as well as impaired self-perceived well-being are considered CHD risk factors (Berry et al, 2012; Buttar et al, 2005; DeSalvo et al, 2006; World Health Organisation, 2002; World Health Organisation, 2004). Hence, in addition to medical treatment and behavioural changes, it can be assumed that HRQoL issues and psychological distress are also important to address. However, knowledge on the key determinants of HRQoL/psychological distress is rather scarce. We investigated the underlying variables associated with a decline in HRQoL/ increase in psychological distress among coronary patients with a particular focus on their cardiovascular risk profile (chapter 5), lifestyle changes (chapter 6) and risk factor level awareness (chapter 7).

Utility scores are often used in health-economic evaluations. Both EQ-5D$_{index}$ scores (EuroQoL utility value) as well as SF-12 based utility scores can be used. However, in order to assess whether these utility instruments are equally suitable, we explored the inter-changeability of these tools (chapter 8). Finally, the usefulness of HRQoL as a policy tool was tested, by performing a cost-utility analysis of secondary cardiovascular prevention (chapter 9).

10.2 MAIN FINDINGS AND DISCUSSION

10.2.1 Reliability and validity of HRQoL/psychological distress measures in CHD patients

As mentioned above, HRQoL/psychological distress instruments are increasingly being used as assessment tools in coronary patients. Although several studies have previously investigated the psychometric properties of HRQoL/psychological distress instruments in various samples of CHD patients, cross-European data are limited (Ellis et al, 2005; Failde et al, 2010; Schweikert et al, 2006; Barth et al, 2005; Cosco et al, 2012). The added value of our study comes from the large sample size, comprising 8,745 patient records from 22 different European countries, providing information on three different instruments simultaneously. Our results support the use of EQ-5D, SF-12 and HADS in European CHD patients. On the whole, all instruments were shown to be valid and reliable for use in coronary patients both on aggregate European level, as well as on country-specific level. Internal consistency, i.e. the degree of homogeneity across items, was confirmed for all three measures, even on country-specific level. It should be noted however, that Cronbach's alpha values were somewhat lower for the EQ-5D$_{index}$ with about half of the countries having a value slightly below 0.70. Two possible reasons for these less acceptable values, could be the heterogeneity among the different EQ-5D items as well as the small number of items giving rise to lower Cronbach's alfa values (Pallant, 2011). Likewise, confirmatory factor analyses showed a good construct validity and known-group discriminative validity was confirmed for all three measures. Constructs capturing similar functional or emotional characteristics correlated highly with one another, supporting convergent validity. Criterion validity was confirmed using the EQ-VAS as well as the SF-12/1 (first question of SF-12 asking about a patient's general health) as overall health criterion. Although, all three tools showed good validity and reliability caution is required as we were not able to assess test-retest reliability and responsiveness.

10.2.2 HRQoL outcomes in coronary patients and associated risk factors

Comparison with the general population

Coronary patients are believed to have an impaired HRQoL/psychological distress. Several studies have indeed reported worse HRQoL outcomes in coronary patients compared to the general population (Boini et al, 2006; Brink et al, 2005; Crilley et al, 2001; Mols et al, 2009; Sprangers et al, 2000; Xie et al, 2008), however in-depth examinations, comparing the HRQoL dimensions of generic instruments are limited (Schweikert et al, 2009; Mols et al, 2009; Mols et al, 2009; Urso et al, 2009). Comparison of EQ-5D outcomes between CHD patients and the general population, across 11 European countries, demonstrated a significant difference. In order to avoid bias due to differences in age distribution between CHD patients and the general population, direct age standardization was performed. Results differed across countries and gender, but overall the greatest HRQoL loss was seen on the anxiety/depression dimension as well as on the EQ-VAS, both in males and females. Furthermore, female coronary patients reported a significantly higher proportion of problems on the mobility (OR=2.00[1.38;2.90]), usual activity (OR= 2.54[1.81;3.57]) and pain/discomfort dimension (OR=1.73[1.23;2.43]) whereas in males, a borderline significant OR was found on the mobility (OR=1.43[0.97;2.11]) and usual activity dimension. No significant difference in the self-care dimension could be observed, neither in males nor in females.

Regarding the SF-12, a theoretical mean value=50 and a standard deviation=10, has been proposed as reference value for both the physical component score (PCS-12) and the mental component score (MCS-12) (Ware et al, 2002). However, in order to reach a valid conclusion about any difference in SF-12 outcomes between CHD patients and the general population, age-specific reference values are needed since HRQoL outcomes are known to evolve with age. We performed some additional analyses (unpublished, see appendix 1), in order to assess whether the EQ-5D findings reported above could be confirmed using the SF-12 instrument. The International Quality of Life Assessment (IQOLA) project has gathered age-specific reference values on 5 of the included EUROASPIRE III countries: France, Italy, the Netherlands, Spain and the UK. According to these reference values, PCS-12 scores worsen with increasing age, whereas MCS-12 outcomes remained stable or improved slightly with increasing age with the exception of Spain and Italy. Only the component measure values were reported, hence we were not able to compare the results on dimension-specific level. Furthermore, no distinction between genders was made. Despite these limitations, the additional analyses allowed us to gain some insight regarding this matter. Three age categories were described by the IQOLA project: 18-44 years; 45-64 years and 65-74 years. Conform with the EQ-5D analyses, we did not include the youngest age category. Analyses were conducted in a similar manner as the previously performed EQ-5D analyses. Conform with the EQ-5D results, some variation was seen across countries. Overall, a significant difference was found between CHD patients and the general population both on the PCS-12 score (-3.49 [-6.00, -0.99]) and the MCS-12 score (-2.29 [-3.65, -0.93]).

A closer look at the HADS results revealed that 27% of male CHD patients and 44% of females CHD patients had a HADS-anxiety (HADS-A) ≥8, and 21% of male CHD patients and 32% of female CHD patients had a HADS-depression (HADS-D) ≥8 (Pajak et al, 2013). Country-specific scores for the general population are however scarce. Within our knowledge age and gender-specific reference values were only available for Germany (Hinz et al, 2011). Comparison of German reference data with the German CHD sample, revealed significantly higher proportion of elevated HADS-A and HADS-D scores in female but not in male CHD patients.

The above presented results have indicated greater relative impairments in female CHD patients compared to males. Furthermore both physical en mental components were affected. EQ-5D comparison revealed significant impairments in CHD patients, on all dimensions with the exception of self-care (both genders) and pain/discomfort (in males).

Non-modifiable risk factors

Detailed analyses of the risk factors associated with an impaired HRQoL/psychological distress in CHD patients designated gender as a key variable, with female patients having worse HRQoL outcomes (Brink et al, 2005; Duenas et al, 2011; Emery et al, 2004; Norris et al, 2008; Norris et al, 2010; Phillips-Bute et al, 2003; Sevinc et al, 2010, Pajak et al, 2013).

Similar findings have been reported in the general population, suggesting existing differences before any event occurs (Martinelli et al, 2008). However, the relative impairment was greater in women, indicating a greater self-perceived impact of CHD on HRQoL in females. Several determinants, explaining the differences in gender have been suggested, however many causes are not well understood and research is still on-going. During childhood, boys and girls have similar HRQoL outcomes, but with increasing age, the HRQoL outcomes in girls deteriorate more rapidly than in boys, resulting in significantly worse outcomes in female adolescents (Michel et al, 2009). Women are known to verbalize more, consequently it might be assumed that women tend to over-report their problems during interview whereas males tend to trivialize (Martinelli et al, 2008). This idea is in contrast with some studies stating that both sexes report their symptoms accurately (Macintyre et al, 1999; Merrill et al, 1997). Some argue however, that women might perceive symptoms in a different way (Norris et al, 2010; Phillips-Bute et al, 2003; van Wijk et al, 1997). Although results indicate that both male and female coronary patients experience the same symptoms, some studies found differences in the proportions of symptoms, with women reporting more angina, pain, nausea, fatigue, syncope, weakness, depression and loss of appetite (DeVon et al, 2002; DeVon et al, 2003; Kimble et al, 2003). Physiologic differences could be one of the reasons why women experience worse HRQoL outcomes. Females have for example smaller coronary arteries, which might increase ischemia (Lichtman et al, 2008). Furthermore, the higher depression rates in women are strongly associated with poorer recovery rates possibly leading to impaired HRQoL results (Lichtman et al, 2008; Norris et al, 2008). In addition, compared to men, women often have a lower sense of coherence (SOC, i.e. experiencing the world as comprehensible, meaningful and manageable) which is significantly associated with a worse HRQoL (Bergman et al, 2012; Eriksson et al, 2006). In addition, some identified social support (meeting and talking regularly with friends and family) as an important predictor of HRQoL in cardiac women (Emery et al, 2004; Norris et al, 2008). The continuing demands in the home environment are also proposed as a possible explanation for worse HRQoL outcomes (Emery et al, 2004). According to Charmaz (1995) the HRQoL outcome can also depend on how patients deal with their illness. Women struggle with an illness, by adapting to the changed circumstances, hence they are more likely to recognize their illness and report about the associated symptoms, whereas men struggle against the illness, trying to deny that anything has changed, hence reporting fewer symptoms (Brink et al, 2005; Charmaz, 1995).

Further investigation of the underlying variables responsible for the decline in HRQoL indicated geographical region as a predictor, with lower HRQoL estimates in CHD patients from eastern European countries. Similar results were seen in a study from the EuroQol Group, with lower HRQoL outcomes in less prosperous countries (The EuroQol Group's International Task Force on Self-Reported Health, 2004). As stated by the EuroQol Group, “Some populations may be more reluctant to give positive answers to the questions in a survey than others”, hence cultural differences might underlie these differences, but also differences in medical practice can be responsible for these observations. Moreover, the patients included in EUROASPIRE III are not always representative for the coronary patients within their country, hence a part of the across country differences might be induced by the study design.

In agreement with previous research, younger patients reported significantly better HRQoL outcomes (The EuroQol Group's International Task Force on Self-Reported Health, 2004; Brink et al, 2005; Lee et al, 2012; Pragodpol et al, 2012; Schweikert et al, 2009) with the exception of the anxiety component, on which younger patients reported more problems (Hinz et al, 2011; Spinhoven et al, 1997; Xie et al, 2008). Again, these findings are not restricted to CHD patients. Worse HRQoL outcomes have also been associated with increasing age in de general population (The EuroQol Group's International Task Force on Self-Reported Health, 2004; Golicki et al, 2010; Hinz et al, 2011; Saarni et al, 2006), which seems quite logical, since the aging process is associated with physical and mental deterioration.

Similar to the results reported by Lee et al. (2012), lower educated patients were found to have significantly poorer HRQoL outcomes. Education can be seen as a proxy for socio-economic status (SES), which is related to lower health status. Evidence suggests that low educated persons have poorer health habits, an increase in comorbidities and worse access to health care facilities (Burstrom et al, 2001; Pappa et al, 2009). Veentra et al (2004) further observed that the HRQoL in lower educated coronary patients was less likely to improve following invasive coronary procedures.

Conform with previous research significantly better HRQoL scores were found in patients undergoing revascularization as recruiting diagnosis (Kim et al, 2005; Lukkarinen et al, 2006; Sevinc et al, 2010; Weintraub et al, 2008). This is most likely caused by a reduction in symptoms related to angina (Kim et al, 2005). Furthermore, as expected various comorbidities, such as diabetes, history of stroke or recurrent coronary events since the index event were associated with worse outcomes (Leach et al, 2011; Peterson et al, 2006; Schwander et al, 2009; Xie et al, 2008).

Metabolic risk factors

With the exception of body mass index (BMI), uncontrolled metabolic risk factors were not or not strongly associated with HRQoL. An uncontrolled total cholesterol (TC) was not associated with HRQoL, with the exception of the MCS-12 and EQ-VAS (borderline), where a significant, but very small gain in HRQoL was observed in controlled patients. Similarly, no significant association between HRQoL and cholesterol was found in the literature (Sevinc et al, 2010). (Khanna et al, 2012; Lau et al, 2004; Lee et al, 2012). In contrast, an uncontrolled BP seemed to be associated with better HRQoL outcomes. This association was however eliminated after adjustment for medication intake. Indeed, about 28% of the EUROASPIRE III patients were taking nitrates and 30% were taking diuretics at the time of the interview, medication which is often prescribed in patients with angina and heart failure respectively (Herlitz et al, 2005; Pragodpol et al, 2012). It is assumed that HRQoL impairments associated with angina and heart failure will improve when medically treated, leading to an unexpected higher HRQoL despite an uncontrolled BP. Contrasting results have been found in the literature, with some reporting a correlation between worse HRQoL and elevated BP, whereas others did not find any association (Carvalho et al, 2012; Herlitz et al, 2005; Sevinc et al, 2010; Soini et al, 2010). With regard to glucose levels, results were inconsistent, with glycated haemoglobin (HbA1c) but not fasting glucose being significantly associated with

HRQoL in patients with diabetes. Khanna et al (2012), found similar results with a significant association between elevated HbA1c values and worse HRQoL outcomes, whereas Lau et a (2004), only found a significant association with the mental HRQoL components. Lee et al (2012) did not find any association with blood glucose. No explanation can be given with regard to the inconsistency between HbA1c and blood glucose. In accordance with the literature, BMI was inversely associated with HRQoL, with obese patients having inferior HRQoL outcomes (Oreopoulos et al, 2010; Schweikert et al, 2009). In contrast, regarding the actual weight change, no significant difference was found in HRQoL outcomes (except for PCS-12) between those who had lost weight (≥5% weight loss), maintained their weight level (±5% weight change), or gained weight (≥5% weight gain) between the recruiting diagnosis and the interview.

Behavioural changes

In accordance with general population findings (Piper et al, 2012; Sarna et al, 2008), in-depth analyses of the association between HRQoL/psychological distress and smoking, revealed better outcomes for never smokers and ex-smokers both on their self-perceived physical and mental health. In coronary patients however, conflicting results have been reported in the past (Haddock et al, 2003; Quist-Paulsen et al, 2006; Schweikert et al, 2009; Taira et al, 2000). Within the EUROASPIRE sample, the time since smoking cessation was not significantly related to HRQoL/psychological distress. Likewise, Piper et al. (2012) have shown rapid HRQoL improvements (1 year) after smoking cessation which sustained for at least 3 years whereas in the Nurses' Health Study, HRQoL scores improved gradually with longer time since quitting (Sarna et al, 2008). Especially the mental health component in prior smokers seemed to be significantly better compared to current smokers. This result was confirmed by others (Mulder et al, 2001). Likewise and in complete agreement with past research, both in the general population as well as in coronary patients, the physical activity level in CHD patients was also associated with HRQoL/psychological distress, with better outcomes in physically active patients (Bize et al, 2007; Sevinc et al, 2010; Romain et al, 2012). Both the attempts undertaken to increase physical activity as well as the actual physical activity levels were associated with better outcomes. These components seem to reinforce one another, with the best scores seen in patients residing in the highest IPAQ class who had moreover made an attempt to increase their physical activity. Attempts to alter dietary behaviour were also associated with HRQoL/psychological distress, with better outcomes in patients who tried to reduce fat and salt intake and increase fish, fruit, and vegetable intake, especially on the overall HRQoL and physical dimensions but less on the mental dimension. Similar results were seen in the SUN project, with an important association between adherence to Mediterranean diet (consumption of fruit, vegetables, and fish and olive oil and reduction of meat and dairy intake) and better SF-36 scores (Henriquez Sánchez et al, 2012). In conclusion, it seems that the act of exercising and healthy eating behaviour themselves, and not merely losing weight, are aligned with better outcomes.

Due to the cross-sectional design of our study, we were unable to assess causality. Are those patients with a better HRQoL/psychological distress more likely to change their behaviour accordingly, do behavioural changes have an influence on a patient's HRQoL/psychological distress, or is there a mutual influence or an external factor leading to both an increase in HRQoL/decrease in psychological distress and increase in physical activity (Romain et al, 2012)? According to the transtheoretical model, behavioural changes can be divided in five different stages of change (Prochaska et al, 1983; Romain et al, 2012). First there is the precontemplation stage, when the individual has no intention to change. The second stage is the contemplation stage, when the individual has the intention to change within the next 6 months. The third stage is the preparation stage, when the individual is intending to change within the next 30 days. Subsequently, individuals can move to the action stage when the individual is being engaged in the behaviour for <6 months. Finally the maintenance stage is achieved when the individual sustains in the change over time. Investigating the association between the different stages of change and HRQoL can be helpful in order to gain insight about the causality between behavioural changes and HRQoL. The EUROPASPIRE III interview contained questions about the intention of patients to change their behaviour. Patients smoking at the time of the interview were asked about their smoking cessation behaviour (no and I do not intend to; yes within the next 6 months; yes within the next 30 days; yes I have quit <6 months; yes I have quit >6 months). Likewise patients were asked about their intention to lose weight (no; yes within the next in the 6 months; yes within the next 30 days; yes I have been trying in the past month). Moreover patients were asked if they exercised regularly (no and I do not intend to; no but I intend to in next 30 days; no but I intend to in next 6 months; yes for less than 6 months; yes for more than 6 months).

In persistent smokers, no significant differences in HRQoL outcomes were found between patients considering smoking cessation versus those not intending to quit, hence it is unlikely that those willing to quit smoking had a higher initial HRQoL allowing them to find the motivation to quit. Likewise, the intention to become physically active was not associated with HRQoL, except in overweight and obese patients, where having no intention to become physically active was associated with poorer HRQoL outcomes, although the differences were small. Not surprisingly, the greatest HRQoL differences were found in the items capturing the current physical health status (PCS-12). After all, physical activity is an important component of HRQoL. Patients experiencing problems with their physical health, due to pain/discomfort for instance, may be less likely to become physically active. These findings support the hypothesis of a vicious circle, where overweight and obese people, known to experience more difficulties in walking or climbing stairs, for example, are less inclined to become physically active, with a higher possibility to have an increase in weight, which can in his turn lead to less exercise (Bauman et al, 2012). Hence, implementing multimodal interventions, focusing both on exercise, diet and weight may be necessary. Furthermore, in overweight and obese patients, no differences were found between those intending to lose weight versus those not intending, except on the PCS-12, on which non-intenders scored better. These results indicate worse HRQoL outcomes in the precontemplation, contemplation or preparation phase, and better outcomes in the action and maintenance phase. This suggests that the lifestyle changes are responsible for an improved HRQoL and not the other way round. Similar results have been found by others investigating the link between the stages of behavioural change and HRQoL (Laforge et al, 1999; Lee et al, 2006; Romain et al, 2012). Nonetheless, it remains possible that patients in the precontemplation, contemplation or preparation phase differ in several unmeasured characteristics from those in the action or maintenance phase, hence these results should be interpreted with caution.

Furthermore, an increase in the number of uncontrolled metabolic and behavioural risk factors (raised BP, raised TC, current smoking, low physical activity and central obesity) was significantly associated with worse HRQoL outcomes, reaffirming the high importance of a holistic approach regarding risk factor prevention.

Awareness

Following the above described context, some authors argue that the awareness of having an increased cardiovascular risk, might result in worse HRQoL outcomes, also known as “the labelling effect” (Mena-Martin et al, 2003). Being aware of an elevated morbidity or mortality risk can induce feelings of anxiety and depression. Indeed, as shown by Mena-martin (2003), hypertensive patients being aware of their condition have worse HRQoL outcomes compared with hypertensive patients not being aware. Likewise, a higher sick leave is reported in such patients (Leynen et al, 2006). Within EUROASPIRE III however, an inverse relationship was found, with patients being aware on at least one risk factor level (BP, TC, blood glucose), having significantly better HRQoL/psychological distress outcomes, compared to those not aware of their risk factor levels. It can be argued that coronary patients already received a “labelling-effect” at the time of their recruiting diagnosis, hence they are all aware of their increased CHD risk. The hypothesis of a labelling effect is therefore not applicable within this context. Another mechanism seems to be play here. The association between risk factor level awareness and better HRQoL/psychological distress outcomes was seen both in patients with a BP, TC or blood glucose on or above target. The relationship between awareness and HRQoL/psychological distress seems to be partly mediated by the attempt of patients to adopt a healthier behaviour. Patients with a greater awareness are more likely to have made attempts in improving their lifestyle. And as discussed above, lifestyle improvements have been shown to be associated with patients’ HRQoL/psychological distress outcomes (Ludt et al, 2011). Nevertheless, there also seems to be a direct link between awareness and HRQoL/psychological distress, in particular with the mental component. Patients who are more aware, feel less anxious and depressed and score better on their mental and emotional well-being regardless of whether they change their lifestyle behaviour. One possible explanation might be that patient involvement in their care and awareness of their risk factor profile could possibly affect their illness perception and sense of control. Poor illness perception and low sense of control have been associated with worse physical and mental outcomes (Lau-Walker et al, 2009; Stafford et al, 2009). Hence, in addition to improved adherence to lifestyle changes, a better sense of control might also lead to a decrease in anxiety (French et al, 2005). Due to the cross-sectional study design of our dataset, we were however not able to assess causality. Hence, there could also be a reverse causality , with better HRQoL outcomes ensuring a greater interest of patients in their own risk factor profile. Patients with less anxiety or depression and a better health status might be more receptive to listen and to remember their risk factor levels. Most likely, some interplay exists between the above described pathways reinforcing one another. Despite risk factor level awareness being positively associated with HRQoL/psychological distress, insufficient awareness rates among

CHD patients were observed. About 82% of patients indicated to be aware of their own BP level, 47% of patients indicated to be aware of their own TC level and 44% of the complete sample indicated to be aware of their blood glucose level, whereas in diabetes patients blood glucose level awareness reached 82%. Those patients not aware about any of their risk factor levels, were more likely to have a lower education, to be low physically active or to be a smoker, whereas those aware on some or all of their own risk factor levels were more likely to have diabetes, to be obese, to have an elevated TC, BP, or blood glucose level. Hence, our results seem to suggest that patients with increased risk factor levels are more likely to be aware of their TC, BP or blood glucose level.

There is a growing interest in the concept of 'Patient Empowerment'. The rationale is that patients take charge of their own health. Small et al, conceptualized empowerment in patients with long-term conditions as: *"an enabling process or outcome arising from communication with the health care professional and a mutual sharing of resources over information relating to illness, which enhances the patient's feelings of control, self-efficacy, coping abilities and ability to achieve change over their condition"(Small 2012).* According to Calvillo and colleagues (2013), four milestones can be considered in the evolution to patient empowerment. The first step is to make patients aware of their condition and to inform them. There is a change from passive to active participation in the disease treatment. When the patient is aware about his/her own health status, proper action plans and guidance can result in better adherence to treatment plans and consequently better health outcomes.

10.2.3 Clinical relevance of HRQoL differences

Due to the large sample size of the EUROAPSIRE III survey, there is a risk that the study is somewhat overpowered, resulting in statistically significant differences that are not necessarily clinically meaningful. Little is know about the clinical relevance of changes in HRQoL, since no general consensus is available on what is perceived as a meaningful difference. Some authors have suggested half a standard deviation as the minimal important difference (MID) (Norman et al, 2003), while others have proposed a 3–5-point change for the SF-12 (Samsa et al, 1999), a MID of 0.074 for EQ-5D (Walters et al, 2005), and a MID of 1.5 for HADS (Puhan et al, 2008).

When we apply these MID's in order to interpret our results we observe a great variation across risk factors. A clinical relevant difference in PCS-12 and EQ-VAS was found between the lowest and highest age categories. Likewise, differences in PCS-12 and MCS-12 seemed to be clinically relevant across the lowest and highest educated patients. Furthermore the impact of diabetes on the PCS-12 and of stroke on the PCS-12 and EQ-VAS was clinically meaningful. Although smoking cessation was significantly associated with HRQoL, the changes were limited and did not reach the MID's. Likewise, dietary changes did not seem to be clinically important. Physical activity on the contrary was associated with clinically meaningful improvements in HRQoL, with the greatest changes seen on the PCS-12 and the EQ-VAS. The increase in number of risk factors was associated with very important differences on all HRQoL domains, especially with regard to the physical component.

10.2.4 How HRQoL can be used in practice

Thus, in addition to the beneficial effect of optimal CHD risk factor control on morbidity and mortality outcomes (Perk et al, 2012), it seems that an optimally controlled CHD risk factor profile has also a favourable influence on a coronary patient's HRQoL. The positive effects of optimal prevention are not only of importance for the individual but also for the society. Scarce health care resources have led to the development of health economic evaluations, used as decision making tool in order to maximize health benefits with the available financial means. These analyses include both benefits and costs related to a given treatment option. Costs include both expenses related to therapy and saving related to avoided morbidity and mortality whereas gains are often expressed as quality adjusted life years (QALY's). QALY's are calculated by multiplying a utility value (degree of self perceived health) with the number of life years a patient is in that particular health state. Utilities usually range between 0 (death) and 1 (perfect health) – although values below 0 exist (health states that are perceived worse than death). Within this thesis we aimed to asses whether optimized secondary prevention, based on the European guidelines on cardiovascular prevention (De Backer et al, 2003), in coronary patients is cost-effective across eight EUROASPIRE III countries (Belgium, Bulgaria, Croatia, Finland, France, Italy, Poland, and the UK). A tailor-made approach was used, estimating patient's future risk, based on their individual risk profile.

EQ-5D utility values, as well as SF-12 derived utility values – also known as SF-6D values, i.e. 6-dimensional health state classification – can be used in health economic evaluations. As reported by Joore et al (2010), differences among both measures can lead to different health economic outcomes. Similar to previous studies in various populations, the EQ-5D$_{index}$ outcomes in the EUROASPIRE sample are significantly correlated with the SF-6D values, with ICC's indicating moderate agreement between the instruments (Brazier et al, 2004a; Ferreira et al, 2008; Kontodimopoulos et al, 2011). However, significant differences remain between both outcomes, making them not simply interchangeable. Across all EUROASPIRE III countries, the median utility values differed significantly from each other with SF-6D utility scores being systematically lower than EQ-5D$_{index}$ outcomes, both at country specific level, as well as after stratification by patient characteristics. Furthermore, a ceiling effect was observed in the EQ-5D instrument, but no floor effect was seen on either instrument. These results are similar to previously reported outcomes (Joore et al, 2010; van Stel et al, 2006), (Bharmal et al, 2006) and Brazier et al. acknowledge a possible ceiling effect of the EQ-5D and a possible floor effect of the SF-6D instrument (Brazier et al, 2004a). Subanalyses in the EUROASPIRE III population revealed that patients reporting no problems on the EQ-5D still reported substantial problems on the SF-6D role limitation and vitality dimensions. This is in line with the lower correlations seen between the EQ-5D dimensions and the SF-6D role limitation and vitality dimension. Furthermore, within our population, especially mental problems are not completely captured by the EQ-5D instrument. Likewise, in the study by Brazier et al. (2004), based on 7 patient groups, it was observed that those patients with full health on the EQ-5D may still experience problems in SF-6D physical functioning, mental health and vitality (Brazier et al, 2004a).

As mentioned by others, some of the differences between the instruments might be explained by the theoretical construction of the measures (Brazier et al, 2004a; Bryan et al, 2005; van Stel et al, 2006). First of all, the recall period is different: ‘today’ versus ‘past four weeks’, however we agree with Van Stel et al. (2006), that the influence of the recall period on the utility differences might be non-significant within our population as it concerns stable CHD patients. Furthermore, the EQ-5D covers only 5 dimensions/questions with 3 answer categories each, whereas the SF-6D captures 6 dimensions, based on 11 SF-12 questions with 3 to 5 response categories each. An increase in number of questions and answers automatically leads to a more descriptive and sensitive tool with a higher amount of possible outcomes. Likewise, the formulation of the question differs across different HRQoL tools. A patient who has sometimes frightened feelings, might for example indicate *“I’m not anxious or depressed”* on the EQ-5D whereas on the SF-12 the patient might tick the box ‘a little of the time’ when asked *“have you felt downhearted and depressed”*. This is only one example of how slightly different questions with different answer possibilities can lead to different outcomes. The more refined answer options of the SF-12 make the tool more sensitive, however, conversion from SF-12 to SF-6D is associated with loss in sensitivity, particularly due to the small range of possible utility scores. The SF-6D outcomes range between 0.296 and 1, which is almost half of the possible EQ-5D range. Hence, SF-6D outcomes are more centred to the middle and the potential difference between health states is larger using the EQ-5D utility scores. This was also reported in a paper by McDonough et al. (2007), concluding that cost-effectiveness analyses using the SF-6D give less favourable cost-effectiveness results (McDonough et al, 2007). On the other hand, the EQ-5D outcomes are very much skewed to the right, hence the probability of having worse outcomes is rather low, with limited room for improvement especially in patients with a mild condition. The SF-6D might be more sensitive for smaller impairments and therefore, the impairments associated with a mild condition might be better recognized by the SF-6D, which can in his turn lead to better cost-effectiveness outcomes. Indeed, the change in utility score rather than the absolute value of the score is of most importance in cost-effectiveness analyses. In agreement with the literature, EUROASPIRE III results have indicated that patients with worse EQ-5D outcomes were more likely to have better SF-6D results, whereas patients with better EQ-5D outcomes were more likely to have worse SF-6D results (Joore et al, 2010). Such inconsistencies among HRQoL tools can result in remarkable and important differences in cost-effectiveness outcomes.

Despite the discussion concerning different cost-utility outcomes, depending on the utility measure used, the general advice on cost-utility analyses is to make use of EQ-5D utility values whenever possible (National Institute for Health and Care Excellence, 2013). And although comparing the cost-utility outcomes based on both utility techniques would be of great value, within this thesis the cost-effectiveness analysis is based on EQ-5D outcomes. Literature data on SF-6D values are less widespread and within our knowledge penalty values associated with developing different cardiovascular conditions are not available. Overall, the cost-effectiveness analyses for the eight countries included, showed mainly favourable results with an average incremental cost-effectiveness ratio (ICER) of €12,484/QALY (the cost-effectiveness threshold is commonly set at 30,000€/QALY). Only in the minority of patients at the lowest risk for recurrent events, intensifying preventive therapy seems not cost-effective. Also, the single impact of intensified cholesterol control seems less cost-effective, possibly because their initial 2-year risk was already fairly low, hence the room for improvement is rather limited. These results underscore the societal value of optimizing prevention in most patients with established CHD, but also highlight the need for setting priorities towards patients more at risk and the need for additional studies comparing intensified prevention with usual care in these patients. However, caution is required when interpreting the results, since the use of SF-6D values might result in different outcomes.

10.3 LIMITATIONS

In order to correctly interpret the results discussed above, some limitations have to be addressed. The major limitation of the EUROASPIRE III study is its cross-sectional design. To start, the design made it infeasible to test responsiveness – i.e. to test the sensitivity of the instruments to changes in health status over time – and to determine test-retest reliability – i.e. to test reproducibility. Secondly, and perhaps even more important, the lack of longitudinal data made it hard to assess causality. Although we were only able to test associations, we made several efforts to give an indication about the most likely direction. With regard to lifestyle changes for example, we investigated whether there was a difference in HRQoL/psychological distress among patients with and without any intention to change their behaviour, in order to examine whether lifestyle changes improve patient's HRQoL/psychological distress or whether it is more likely that an improved HRQoL/psychological distress will result in behavioural changes.

Furthermore, the results discussed above are mainly based on self-reported data. The main disadvantages of this way of data collection are recall bias and social desirability bias. The first arises when patients are asked to report on experiences, behaviour and events from the past, the latter occurs when patients are inclined to give a more socially acceptable image of themselves. Social desirability bias has been frequently associated with self-reported behaviour (Adams et al, 2005; Scagliusi et al, 2003; Tooze et al, 2004). Within EUROASPIRE III, the included questions did not allow objective assessment of the degree to which an attempt was made to alter their behaviour, hence it is likely that patients have overestimated their dietary changes, physical activity changes and smoking cessation attempts since their recruiting diagnosis.

CHD patients included in the survey, were mainly identified from academic hospitals, situated in selected geographical areas. The participating countries represent different geographical areas across Europe with large differences in the organization of medical care and economic resources. Only those areas with a large defined population (> half a million of people) were selected. Within the selected area, at least one hospital offers interventional cardiology and cardiac surgery and one or more hospitals offer acute care for patients with acute myocardial infarction and ischemia. Hence, they are not a representative sample of all CHD patients in each country. It is likely that the average CHD profile is even worse with higher TC levels, higher BP levels, higher glucose levels, worse behavioural risk factors, worse awareness levels, poorer HRQoL and more psychological distress.

Data collection at interview was organized in a standardized way with structured questionnaires and standardised methods of measurement. Additional information about the recruiting diagnosis was collected from the available medical records, hence completeness and accuracy were dependent on collection methods used by doctors and nurses at that time. Furthermore, about 27% of patients eligible for study-inclusion did not participate to the interview. The most common reasons for not being interviewed were refusal to participate or no response (39.4%), patient's death (14.9%), change in patient's location (10.1%) and change in health status (6.2%) (Kotseva et al, 2009b). Those patients, unwilling to complete the questionnaires were most probably those with a worse health status, and worse HRQoL. It is very likely that the above reported results are an underestimation of the true number of patients with an impaired HRQoL; hence this limitation might be the greatest cause of bias in this thesis.

The research questions in this thesis were not the main focus of the EUROASPIRE III survey. Three self-administered questionnaires on HRQoL and/or psychological distress were included. In order to interpret the results of this thesis it is important to discuss their advantages and disadvantages. EQ-5D and SF-12 are commonly used generic measures of health status, suitable for a wide range of different populations, including coronary patients. The main advantage of these tools, is their ability to compare outcomes across patient groups and to their ability to assess the impact of a disease compared with the general population. On the other hand, generic tools are not always sensitive enough to capture small but clinically significant differences between patients. The MacNew quality of life questionnaire would have been more appropriate to measure small differences between groups (Thompson, 2003; Maes, 2008). Maes and colleagues (2008) also suggest to include a brief anxiety and depression measure for psychosocial assessment when evaluating the outcomes in coronary patients. In EUROASPIRE III, the HADS instrument was used as a measure of psychological distress. The tool is useful as a screening instrument to identify emotional distress but is not adequate for use as a diagnostic tool (Brennan et al, 2010). Furthermore, although we have found two distinct factors based on the confirmatory factor analyses, some other authors were not able to differentiate between anxiety and depression in coronary patients (Martin, 2008). It is important to keep in mind that HADS does not necessarily correspond with what is clinically considered as anxiety and depression. The Patient Health Questionnaire (PHQ-9) or the Beck depression inventory (BDI-II) might be more suitable for assessing depression, since these measures incorporate the DSM criteria for depression (Beck et al, 1996). Some aspects of particular importance in CHD patients might not be captured with these generic instruments. Hence the use of CHD-specific tools can be of additional value, since they are often more sensitive in capturing disease specific impairments. Further research should preferably include generic as well as disease specific tools, e.g. the HeartQol questionnaire, specifically developed for use in CHD patients (Oldridge et al, 2005).

10.4 CONCLUSIONS AND FUTURE DIRECTIONS

Measuring a patient's self-perceived HRQoL/psychological distress is useful both from a patient perspective as well as from a health care provider and policy maker perspective. The benefits of medication intake and behavioural changes on metabolic and behavioural risk factors are well-accepted, however less is known on how an impaired HRQoL or psychological distress can be prevented or improved. Great differences have been observed in HRQoL/psychological distress outcomes between patients with the same clinical profile, hence assessing patient's self-perceived health in clinical practice can be useful to identify health needs or to measure disease impact, in order to adjust treatment accordingly.

The EQ-5D, SF-12 and the HADS instrument are valid and reliable for use in CHD patients across Europe. Compared to the general population, both the physical and mental well-being were significantly (both from a statistical and clinical point of view) impaired in CHD patients. Although a great variation was seen across countries, the greatest impairment was observed on the anxiety/depression, mobility, usual activities and pain/discomfort (only in females) dimensions. Future research should investigate the ability of the tools to capture changes and to test reproducibility. Since country-specific normative information is rather scarce, there is a need for a coordinated cross-country collection of HRQoL/psychological distress information, with well-defined inclusion criteria and additional collection of covariates. This will allow easy comparison between the general population and several patient groups (not limited to CHD patients). Furthermore the usefulness of other locally translated and validated tools should be tested, with a particular focus on how outcomes differ from each other depending on the instrument used. These findings might help in formulating guidelines regarding the use of utility values in health economic analyses. A particular interesting instrument to evaluate will be the HeartQoL tool (Oldridge et al, 2005). This tool is developed as a CHD-specific HRQoL questionnaire, with the aim to compare HRQoL outcomes in patients with angina pectoris, MI and heart failure. The instrument has two subscales from which a global score can be calculated. This allows clinicians and researchers to assess baseline HRQoL, to make between-diagnosis comparisons of HRQoL, and to evaluate change in HRQoL in CHD patients. The instrument has been included in the EUROASPIRE IV survey; hence we are eagerly looking forward to these data.

Several CHD risk factors were associated with HRQoL/psychological distress. The best outcomes were seen among those patients with an optimally controlled risk factor profile. A great potential was demonstrated regarding the effect of lifestyle, hence lifestyle interventions should be evaluated regarding their effect on HRQoL/psychological distress. Further research should focus on a longitudinal assessment in order to better understand the direction of the relationship between lifestyle changes and HRQoL/psychological distress. Also, it is unclear whether these benefits in HRQoL/psychological distress are sustained over time or whether the gains are associated with a one-time benefit inherent to the change itself. Hence the long-term gains in HRQoL/psychological distress should be investigated. It might also be worthwhile to explore the effect of cardiovascular medication on HRQoL/psychological distress outcomes, since most CHD patients are taking antihypertensive or lipid lowering medication.

Within clinical practice, particular attention should be given to females and younger patients, less educated patients, and patients with comorbidities, since they are more likely to suffer from an impaired HRQoL/psychological distress. In addition to the individual burden on a patient's live, self-perceived health status is also associated with future mortality and morbidity as well as with increased health care expenses, hence actions to tackle these impairments are needed. Furthermore, patients should be encouraged to adopt a healthier lifestyle, not only will this have a direct influence on metabolic risk factors and hence future health, a healthier lifestyle can also lead to a better HRQoL/psychological distress. Smokers often have concerns about the effect of smoking cessation on their weight, life satisfaction, and HRQoL/psychological distress. Likewise, inactive or obese patients do not always see the benefits of dietary and physical activity lifestyle changes. In order to convince patients in changing their behaviour, doctors and other healthcare professionals should emphasize the improvements in HRQoL/psychological distress seen in patients who adopt a healthier lifestyle. Furthermore, these findings can be important for decision makers when setting the priorities related to their prevention policy.

When using HRQoL outcomes in policy decision making, particular attention should be given to the choice of HRQoL instrument. Although EQ-5D and SF-6D utility values, -often used in health economic evaluations- were shown to correlate significantly, large differences between the measures were found, with median values significantly different from each other. This can pose a real threat on the usefulness and credibility of health economic evaluations.

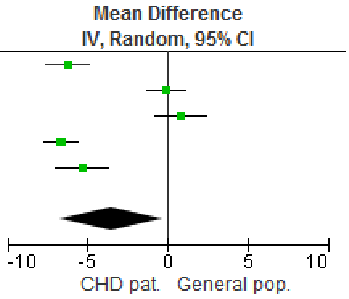
Appendix

Appendix 1: Comparison between the coronary patients and the general population

PCS-12

Study or Subgroup	CHD pat. Mean	CHD pat. SD	CHD pat. Total	General pop. Mean	General pop. SD	General pop. Total	Weight	Mean Difference IV, Random, 95% CI
FRANCE	41.64	9.66	223	47.88	8.41	1235	20.0%	-6.24 [-7.59, -4.89]
ITALY	47.35	8.77	318	47.41	9.05	598	20.2%	-0.06 [-1.27, 1.15]
NETHERLANDS	47.61	9.15	161	46.79	9.97	715	19.8%	0.82 [-0.77, 2.41]
SPAIN	38.88	9.91	409	45.55	10.33	1946	20.3%	-6.67 [-7.73, -5.61]
UK	42.2	11.57	231	47.54	10.85	863	19.7%	-5.34 [-7.00, -3.68]
Total (95% CI)			**1342**			**5357**	**100.0%**	**-3.51 [-6.69, -0.32]**

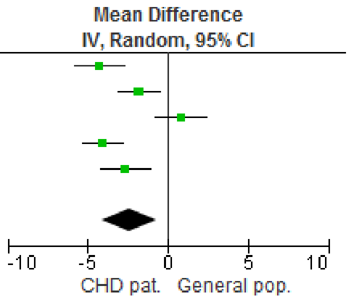
Heterogeneity: Tau² = 12.70; Chi² = 113.06, df = 4 (P < 0.00001); I² = 96%
Test for overall effect: Z = 2.16 (P = 0.03)



MCS-12

Study or Subgroup	CHD pat. Mean	CHD pat. SD	CHD pat. Total	General pop. Mean	General pop. SD	General pop. Total	Weight	Mean Difference IV, Random, 95% CI
FRANCE	44.21	11.34	223	48.48	9.32	1235	19.6%	-4.27 [-5.85, -2.69]
ITALY	45.23	9.05	318	47.05	10.83	598	20.6%	-1.82 [-3.14, -0.50]
NETHERLANDS	52.85	9.48	161	52.01	9.19	715	19.4%	0.84 [-0.77, 2.45]
SPAIN	46.73	12.26	409	50.8	10.05	1946	20.7%	-4.07 [-5.34, -2.80]
UK	49.47	10.85	231	52.14	9.51	863	19.7%	-2.67 [-4.21, -1.13]
Total (95% CI)			**1342**			**5357**	**100.0%**	**-2.42 [-4.14, -0.69]**

Heterogeneity: Tau² = 3.32; Chi² = 28.27, df = 4 (P < 0.0001); I² = 86%
Test for overall effect: Z = 2.75 (P = 0.006)



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Summary

The assessment of patient reported outcomes has gained importance over the latest decades. There is a general consensus that morbidity and mortality rates do not reflect all aspects of health. Indeed, patients' self-perceived emotional, social and physical well-being have received increased attention, especially in long-term chronic conditions, when full recovery is quite unlikely. The goal of today's medicine is therefore not merely to extend a person's life expectancy, but also to ensure a sufficiently high long-term Health-Related Quality of Life (HRQoL). HRQoL measurement has been proven useful in evaluating medical treatment in clinical research, but can just as easily be used in daily clinical practice. Furthermore, HRQoL information can also be helpful for audit purposes, as assessment tool for the quality of delivered health care and in health policy decision making.

Coronary patients are particularly vulnerable to have an impaired self-perceived HRQoL. Their illness is often associated with pain, worrying thoughts, anxiety and depression, physical limitations and social restrictions. The primary purpose of this thesis was to investigate the association between Coronary Heart Disease (CHD) and HRQoL and psychological distress. Analyses were based on the EUROASPIRE III (EUROpean Action on Secondary and Primary Prevention through Intervention to Reduce Events) survey. This cross-sectional study (2006-2007) aimed to determine whether the European recommendations on cardiovascular disease (CVD) prevention were being followed in everyday clinical practice. Patients aged between 18 and 80 years, hospitalized for coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), acute myocardial infarction (AMI) or myocardial ischemia, were retrospectively identified from diagnostic registers, hospital discharge lists or other sources at 76 different hospital centres across 22 European countries: Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, Romania, Russian Federation, Slovenia, Spain, The Netherlands, Turkey, and the United Kingdom (UK). At least 6 months and not later than 3 years after their coronary event, patients were interviewed and clinically examined. During interview patients were asked to complete 3 HRQoL/psychological distress questionnaires: EQ-5D (EuroQol-5D), SF-12 (12-item Short Form health survey) and HADS (Hospital Anxiety and Depression scale).

To start, the validity and reliability of the 3 instruments was assessed. Cronbach's alpha indicated good internal consistency for all measures. Discriminative validity analyses confirmed significant differences between known groups: age, gender, educational level. In addition, all hypothesized correlations between different constructs (convergent validity) and items (criterion validity) were confirmed. Also, good construct validity for HADS and SF-12 dimensions was observed. On country-specific level, results were roughly similar. Based on the EUROASPIRE III data, we can conclude that the EQ-5D as well as the SF-12 and the HADS are reliable and valid instruments for use in a stable coronary population, both on aggregate European level and on country-specific level.

Secondly, if available we compared HRQoL outcomes in CHD patients with age-adjusted values from the general population, with the aim to identify those dimensions mostly impaired. With regard to the EQ-5D a great variation was found across countries (11 countries included). Overall, in comparison with reference values, all EQ-5D dimensions in CHD patients were significantly impaired with the exception of self-care and pain/discomfort (in males). Similarly, significant differences were found between CHD patients and the general population both on the PCS-12 score (SF-12 Physical Component Summary scale) and the MCS-12 (SF-12 Mental Component Summary scale).

Detailed investigation of the association between patients' cardiovascular profile and their HRQoL revealed a large heterogeneity in HRQoL values between countries and patient groups. Worse HRQoL estimates were found in women, older patients, less educated patients, patients with myocardial infarction or ischemia as recruiting diagnosis, patients with a history of stroke and patients who suffered from a recurring CHD event. In addition, HRQoL was significantly associated with current smoking, central obesity, lack of exercise and inappropriate HbA1c control in patients with diabetes. Furthermore, the number of risk factors was inversely associated with HRQoL outcomes.

In-depth analyses investigated the link between lifestyle changes and HRQoL/psychological distress. Both smoking cessation, increase in physical activity and dietary changes were significantly associated with a better outcome. The lack of association between the intention to accept a healthier lifestyle and patients' HRQoL/psychological distress most likely indicates that the lifestyle changes induce better HRQoL/psychological distress outcomes and not the other way round.

Additionally, suboptimal risk factor level awareness rates were found. Whereas about 82% of patients indicated to be aware of their own blood pressure level, only 47% of patients indicated to be aware of their cholesterol level. Furthermore, only 44% of patients were aware of their blood glucose level, whereas in diabetes patients blood glucose level awareness reached 82%. A greater risk factor level awareness was significantly associated with better HRQoL/psychological distress. Not only are patients with a greater awareness more likely to have made attempts in improving their lifestyle, there also seems to be a direct link between awareness and HRQoL/psychological distress, in particular with the mental component. It is hypothesized that patient involvement in their care and patient awareness of their risk factor profile could possibly affect their illness perception and sense of control.

The inter-changeability between the EQ-5D and the SF-12 measures was assessed in our sample of coronary patients. Both measures allow calculating a utility value, which can be used in health-economic evaluations. Past research indicated that differences in utility measures used can lead to different results with better or worse cost-effectiveness outcomes, depending on the instrument used. This can pose a real threat on the usefulness and credibility of health economic evaluations. Our results indicate a significant correlation between EQ-5D and SF-12 (6 dimensional health state classification - SF-6D) utility values, however, large differences between the two measures remain. About 28.8% of patients reported a ceiling effect on the EQ-5D instrument, whereas only 4.2% of patients reported full health based on the SF-6D. Especially the mental component does not seem to be completely captured by the EQ-5D instrument. Furthermore, patients with worse EQ-5D outcomes were more likely to have better SF-6D results, whereas patients with better EQ-5D outcomes were more likely to have worse SF-6D results, hence within our population, the measures were not interchangeable. Furthermore, as an example of how HRQoL can be used in practice, the individual EQ-5D utility outcomes from the EUROASPIRE III sample were applied to assess the cost-effectiveness of optimal cardiovascular prevention in coronary patients, which can be helpful in health policy decision making. Overall, the cost-effectiveness analyses for the eight countries included in the analyses, showed mainly favourable results with an average incremental cost-effectiveness ratio (ICER) of €12,484 per Quality Adjusted Life Year (QALY). Only in the minority of patients at the lowest risk for recurrent events, intensifying preventive therapy seems not cost-effective. Also, the single impact of intensified cholesterol control seems less cost-effective, possibly because their initial 2-year risk was already fairly low, hence the room for improvement is rather limited. Comparing the cost-utility outcomes, based on the EQ-5D utilities on the one hand and the SF-6D utilities on the other, would be of great value. However, literature data on SF-6D values are less widespread and within our knowledge penalty values associated with developing different cardiovascular conditions are not available, hence we were not able to perform this comparison.

Within clinical practice, particular attention should be given to the self-perceived health status of females and younger patients, less educated patients, and patients with comorbidities. In addition to the individual burden on a patient's live, self-perceived health status, anxiety and depression are also associated with future mortality and morbidity as well as with increased health care expenses, hence actions to tackle these impairments are needed. Patients should be encouraged to adopt a healthier lifestyle, not only will this have a direct influence on metabolic risk factors and hence future health, a healthier lifestyle can also lead to a better HRQoL/psychological distress. Smokers often have concerns about the effect of smoking cessation on their weight, life satisfaction, and HRQoL. Likewise, inactive or obese patients do not always see which benefits could be given by their dietary and physical activity lifestyle changes. In order to convince patients in changing their behaviour, doctors and other healthcare professionals should emphasize the improvements in HRQoL/psychological distress seen in patients who adopt a healthier lifestyle. Furthermore, these findings can be important for decision makers when setting the priorities related to their prevention policy.

Samenvatting

De evaluatie van patiënt gerapporteerde uitkomsten heeft aan belang gewonnen gedurende de laatste decennia. Er is een algemene consensus dat ziekte en sterfte niet alle aspecten van gezondheid weergeven. De subjectieve ervaring van de patiënt zijn emotionele, sociale en fysieke welzijn heeft meer aandacht gekregen, voornamelijk in langdurige chronische aandoeningen waarbij volledig herstel zeer onwaarschijnlijk is. Het doel van geneeskunde is dus niet enkel om de levensduur van patiënten te verlengen, maar ook om te zorgen voor een voldoende hoge gezondheidsgerelateerde kwaliteit van leven (HRQoL). Het meten van HRQoL is nuttig gebleken bij de evaluatie van medische behandeling in klinisch onderzoek, maar kan ook gebruikt worden in de dagelijkse klinische praktijk. Verder kan HRQoL informatie ook bruikbaar zijn bij het uitvoeren van audits, als toetsingsinstrument voor de kwaliteit van de geleverde zorg en bij de besluitvorming binnen het gezondheidszorgbeleid.

Coronaire patiënten zijn bijzonder vatbaar om een verminderde HRQoL te ervaren. Hun aandoening is vaak geassocieerd met pijn, piekeren, angst en depressie, fysieke en sociale beperkingen. Het primaire doel van dit proefschrift is om de associatie tussen hartziekte en HRQoL/psychologisch welzijn te onderzoeken. De analyses zijn gebaseerd op de EUROASPIRE III (EUROpean Action on Secondary and Primary Prevention through Intervention to Reduce Events) survey. Deze cross-sectionele studie (2006-2007) had als doel na te gaan of de Europese aanbevelingen inzake cardiovasculaire preventie werden opgevolgd in de dagdagelijkse klinische praktijk. Patiënten tussen 18 en 80 jaar oud, gehospitaliseerd voor een coronaire bypass (CABG), een percutane coronaire interventie (PCI), een acuut myocardinfarct (AMI) of een myocardiale ischemie, werden retrospectief geïdentificeerd via diagnostische registers, ontslaglijsten van ziekenhuizen of andere bronnen via 76 ziekenhuizen in 22 Europese landen: België, Bulgarije, Kroatië, Cyprus, Tsjechië, Finland, Frankrijk, Duitsland, Griekenland, Hongarije, Ierland, Italië, Letland, Litouwen, Polen, Roemenië, Rusland, Slovenië, Spanje, Nederland, Turkije en het Verenigd Koninkrijk. Ten minste 6 maanden en maximaal 3 jaar na hun coronaire gebeurtenis, werden de patiënten geïnterviewd en klinisch onderzocht. Tijdens het interview werd aan de patiënten gevraagd om 3 algemene vragenlijsten over hun HRQol/psychologisch welzijn in te vullen: EQ-5D (EuroQol-5D), SF-12 (12-item Short Form health survey) en de HADS (Hospital Anxiety and Depression Scale) .

Eerst werd de validiteit en betrouwbaarheid van de 3 vragenlijsten geëvalueerd. Cronbach's alfa resultaten wijzen op een goede interne consistentie voor de 3 vragenlijsten. Analyses inzake de discriminerende validiteit bevestigden significante verschillen tussen bekende variabelen zoals leeftijd, geslacht en opleidingsniveau. Daarnaast werden alle veronderstelde correlaties tussen verschillende constructen (convergente validiteit) en items (criteriumvaliditeit) bevestigd. Goede constructvaliditeit voor HADS en de SF-12 dimensies werd waargenomen. Vergelijkbare resultaten werden waargenomen op landen-specifiek niveau. Op basis van de EUROASPIRE III data kunnen we concluderen dat de EQ-5D, de

SF-12 en de HADS betrouwbare en valide instrumenten zijn voor het gebruik in een populatie van stabiele coronaire patiënten, zowel op geaggregeerd Europees niveau als op landen-specifiek niveau.

Vervolgens hebben we de HRQoL resultaten van de coronaire patiënten vergeleken met de voor leeftijd-gecorrigeerde HRQoL waarden uit de algemene populatie (indien beschikbaar) om zo de meest aangetaste dimensies te identificeren. Wat betreft de EQ-5D werd een grote variatie vastgesteld tussen de verschillende landen (11 landen werden geïncludeerd). In vergelijking met referentiewaarden, waren alle EQ-5D dimensies in de studiepopulatie significant aangetast, met uitzondering van zelfzorg en pijn/ongemak (bij mannen). Tevens werden significante verschillen gevonden tussen coronaire patiënten en de algemene bevolking op zowel de PCS-12 score (SF-12 Physical Component Summary scale) als de MCS-12 (SF-12 Mental Component Summary scale).

Onderzoek inzake de associatie tussen het cardiovasculair profiel van de patiënten en hun HRQoL toonde een grote heterogeniteit in HRQoL waarden tussen landen en patiëntengroepen. Slechtere HRQoL scores werden gevonden bij vrouwen, oudere patiënten, lager opgeleide patiënten, patiënten met een myocardinfarct of ischemie als initiële diagnose, patiënten met een voorgeschiedenis van een beroerte en patiënten met een terugkerende coronaire gebeurtenis. Daarnaast was HRQoL significant geassocieerd met roken, buikvet, gebrek aan lichaamsbeweging en onvoldoende HbA1c controle bij diabetespatiënten. Bovendien was een stijging in het aantal risicofactoren geassocieerd met slechtere HRQoL.

Gedetailleerde analyses inzake het verband tussen levensstijlveranderingen en HRQoL/psychologisch welzijn toonden aan dat zowel stoppen met roken als een toename van fysieke activiteit en veranderingen in het dieet significant geassocieerd waren met een betere HRQoL/psychologisch welzijn. Aangezien het al of niet de intentie hebben om een gezondere levensstijl aan te nemen niet geassocieerd is met de HRQoL/psychologisch welzijn van patiënten lijkt het zeer waarschijnlijk dat levensstijlveranderingen betere HRQoL/psychologisch welzijn induceren en niet andersom.

Daarnaast bleek bij de patiënten de kennis van hun eigen risicofactoren niveau suboptimaal. Ongeveer 82% van de patiënten gaven aan kennis te hebben van hun eigen bloeddruk waarde, terwijl slechts 47 % van de patiënten zich bewust waren van hun eigen cholesterolgehalte. Bovendien was slechts 44 % van de patiënten op de hoogte van hun bloedsuikerspiegel, terwijl 82% van diabetespatiënten kennis had van hun eigen bloedsuikerspiegel niveau. Een groter bewustzijn van de eigen risicofactor waarden was significant geassocieerd met een betere HRQoL/psychologisch welzijn. Niet alleen hadden patiënten met een groter bewustzijn meer pogingen ondernomen om hun levensstijl te verbeteren, er blijkt ook een direct verband te zijn tussen bewustzijn en HRQoL/psychologisch welzijn, in het bijzonder met de mentale component. Er wordt verondersteld dat de betrokkenheid van patiënten in hun zorg en het bewustzijn van hun risicofactor profiel een invloed zou kunnen hebben op de beleving van hun aandoening en het gevoel van controle.

De uitwisselbaarheid tussen het EQ-5D en SF-12 instrument werd onderzocht in onze steekproef van coronaire patiënten. Beide instrumenten laten toe om een utiliteitwaarde te berekenen, die gebruikt kan worden in gezondheidseconomische evaluaties. Eerder onderzoek gaf aan dat de verschillen tussen beide instrumenten kan leiden tot andere uitkomsten met betere of slechtere kosteneffectiviteit resultaten als gevolg, afhankelijk van het gebruikte instrument. Dit kan een reële bedreiging vormen voor wat betreft het nut en de geloofwaardigheid van gezondheidseconomische evaluaties. Onze resultaten tonen een significante correlatie tussen EQ-5D en SF-12 (6 dimensional health state classification - SF-6D) utiliteitwaarden, maar er blijven echter grote verschillen bestaan tussen de twee instrumenten. Ongeveer 28,8 % van de patiënten rapporteren een plafondeffect op het EQ-5D instrument, terwijl slechts 4,2 % van de patiënten een perfecte gezondheid rapporteren op basis van de SF-6D. Vooral de mentale component lijkt niet volledig te worden omvat door het EQ-5D instrument. Bovendien hadden patiënten met slechte EQ-5D resultaten meer kans om betere SF-6D uitkomsten te hebben en vice versa. Binnen de onderzochte populatie zijn de instrumenten dan ook niet uitwisselbaar. Als voorbeeld van hoe HRQoL kan worden gebruikt in de praktijk werden de individuele EQ-5D utiliteitwaarden van de EUROASPIRE III survey aangewend om de kosteneffectiviteit van optimale cardiovasculaire preventie bij coronaire patiënten na te gaan. Dit kan nuttig zijn in het beslissingsproces van het gezondheidszorgbeleid. De kosteneffectiviteit analyses voor de acht opgenomen landen, toonden voornamelijk gunstige resultaten met een gemiddelde incrementele kosteneffectiviteit ratio (IKER) van € 12.484 per aan kwaliteit aangepast levensjaar (QALY). Alleen bij een minderheid van de patiënten, met de laagste kans om een nieuwe coronair event te krijgen, lijkt het versterken van preventie niet kosteneffectief. De invloed van een louter intensievere cholesterolcontrole lijkt eveneens minder rendabel, wellicht omdat hun aanvankelijk 2-jarig risico al vrij laag was, met dus een beperktere ruimte voor verbetering. Het vergelijken van de kosten-utiliteiten uitkomsten, gebaseerd op enerzijds de EQ-5D utiliteitwaarde en anderzijds de SF-6D utiliteitwaarden, kan van grote waarde zijn. De literatuurgegevens inzake SF-6D utiliteitwaarden zijn echter minder wijdverspreid. Het utiliteitsverlies gepaard gaande met de ontwikkeling van verschillende cardiovasculaire aandoeningen was niet beschikbaar in de literatuur, waardoor we niet in staat waren om deze vergelijking uit te voeren.

Binnen de klinische praktijk zou er bijzondere aandacht moeten worden besteed aan de zelf-ervaren gezondheidstoestand en het psychologisch welzijn van vrouwen en jongere patiënten, lager opgeleide patiënten en patiënten met comorbiditeit. Naast de individuele last is de zelf-ervaren gezondheidstoestand, angst en depressie ook geassocieerd met toekomstige ziekte en sterfte, alsook met hogere gezondheidszorguitgaven. Acties zijn daarom noodzakelijk. Patiënten moeten aangemoedigd worden om een gezondere levensstijl aan te nemen. Dit zal niet alleen een directe invloed hebben op de metabole risicofactoren en bijgevolg hun toekomstige gezondheid, maar een gezondere levensstijl kan ook leiden tot een betere HRQoL/psychologisch welzijn. Rokers piekeren bijvoorbeeld vaak over het effect van rookstop op hun gewicht, hun tevredenheid over het leven en hun HRQoL. Evenzo zien inactieve of zwaarlijvige patiënten niet altijd de voordelen in van een gezond dieet en lichaamsbeweging. Om patiënten te overtuigen hun gedrag te veranderen, moeten artsen en andere zorgverstrekkers de verbeteringen in HRQoL/psychologisch welzijn gelinkt aan een gezondere levensstijlverandering benadrukken. Bovendien kunnen deze bevindingen belangrijk zijn voor beleidsmakers bij het stellen van prioriteiten met betrekking tot het preventiebeleid.

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Ghent, January 2014
Delphine De Smedt

About the author

Delphine De Smedt was born May 2nd, 1983 in the beautiful city of Ghent. Combining a master degree in biomedical sciences (Ghent University- 2006) with a master degree in business economics (Ghent University-2007), she started her career as attaché at the service of health care within the NIHDI (National Institute for Health and Disability Insurance) where she was responsible for maintaining the relationship between care- and revalidation services and the NIHDI. One year later in august 2008, she began working as a researcher at the Ghent University, developing health economic analyses and performing health economic related research within various domains. During that time she co-founded the Belgian ISPOR student chapter, of which she was president during 2 years. In 2010 she started working on the EUROASPIRE III database, on which she continued working during the remainder of her doctoral research. She received the “EUROPREVENT young investigator award” in 2012, assigned by the European Association for Cardiovascular Prevention & Rehabilitation for her work on the association between health related quality of life and the risk profile in coronary patients.

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